Neurochemistry of Consciousness

Edited by
Elaine Perry,
Heather Ashton and
Allan Young

NT
HIS
NE
ENK
SP
Neuromodulators
S-HT
Adenosine
DA
GABA
GLU
ACh

Foreword by Susan Greenfield

Neurochemistry of Consciousness

Advances in Consciousness Research

Advances in Consciousness Research provides a forum for scholars from different scientific disciplines and fields of knowledge who study consciousness in its multifaceted aspects. Thus the Series will include (but not be limited to) the various areas of cognitive science, including cognitive psychology, linguistics, brain science and philosophy. The orientation of the Series is toward developing new interdisciplinary and integrative approaches for the investigation, description and theory of consciousness, as well as the practical consequences of this research for the individual and society.

Series A: Theory and Method. Contributions to the development of theory and method in the study of consciousness.

Volume 36

Neurochemistry of Consciousness: Neurotransmitters in mind
Edited by Elaine Perry, Heather Ashton and Allan Young

Neurochemistry of Consciousness

Neurotransmitters in mind

With a Foreword by Susan Greenfield

Edited by

Elaine Perry
Heather Ashton
Allan Young

University of Newcastle
Newcastle-upon-Tyne

Table of contents

Foreword

Susan Greenfield

The biggest question, arguably, that any scientist or indeed human being can ask, is how the mass of tissue in the brain can generate the inner experience that we call consciousness: the state that no one else can access. However articulate, poetic, musical or close to someone you may be, that elusive subjectivity, — the direct first-hand 'feel' of the sun on your face, or the grass between bare toes, — is quintessentially personal, utterly subjective. This simultaneously elusive, yet intimate phenomenon has, of course, kept droves of philosophers occupied throughout the ages. But it is only in the last ten or twenty years, that science has actually moved in.

Since scientists are trained to be utterly objective, — we don't even use the active voice, but prefer the far more clumsy, passive; 'a solution was made up' for example — it is small wonder that it goes against the grain now to bring the machinery of scientific method to bear against such an intractable target. Hence many scientists, including and particularly brain scientists, tend to distance themselves from this area of study, on the grounds that it is impossible, given current technologies and state of knowledge, to make any progress. As one particular colleague of mine, an expert on Alzheimer's Disease, remarked, "I just take consciousness for granted". On the other hand, if we are to work on the brain, then surely such an approach is indefensible: as the philosopher John Searle remarked, for brain scientists to ignore consciousness is like someone working on the stomach to say they are not interested in digestion.

Other scientists, nonetheless, fascinated by consciousness, simply cannot raise the funds for empirical investigation. Given the mystic-like image the word still conjures up to the mind-set of grant review panels, approaches have been sardonically dubbed 'a career limiting move'. But despite this hostile culture there is, to their credit, a third, growing band of scientists who, nonetheless, are squaring up to the problem. Curiously, however, brain scientists have been conspicuously absent, in the early days, from this group of pioneers. For example the mathematician, Roger Penrose, and the physicist,

Brian Josephson, have made important contributions to the field. Even when bio-medical scientists do take the centre-stage, as in the case of Francis Crick, or Gerry Edelman, an immunologist, they are not necessarily known from their grounding in the basic brain sciences. An interesting feature, however, of the individuals mentioned, is that there is a high proportion of Nobel Prize Winners!

Until now, it seems, only those who already have a strong scientific reputation and, perhaps, the time to reflect on these issues away from the hurly-burly of peer-review papers and grant writing are able to contemplate this biggest, and most exciting question. However, the landscape is rapidly changing, and now an increasing number of neuroscientists are exploring what contributions they can actually make.

We are now looking beyond the stumbling block of causality: the water of neuronal signalling, translated into the wine of subjective experience. The philosopher David Chalmers has referred to this impasse as the 'Hard Problem'. Where neuroscience now might make a contribution, albeit a less glamorous one than coming up with a simple rubric for the conversion, is in showing increasingly sensitive and precise *correlations* of consciousness, i.e. matching up how people feel with what is occurring in the brain.

Given this more realistic goal, it is surprising how the field has previously been dominated by mathematical models of networks of neurons. We know that such neuronal networks are quasi-permanent, slow to form, and highly local within the brain. Although they may be a basis for learning and memory, we know that you can be conscious without learning or remembering anything and, similarly, that computer processes can occur that will modify responses to subsequent stimulus, but at the same time do not entail a conscious experience. If we are to look for a correlation of consciousness, then drugs offer a perfect Rosetta Stone, — after all, by manipulating the chemicals in our brain with certain drugs, we can, on the one hand, report changes in how we feel but, at the same time, match this up with the chemistry of the brain. Moreover, given that psychoactive drugs modify our emotions, and do so by modifying chemicals in the brain, it follows that emotions have a chemical basis. Now we consider that although learning and memory can be dissociated from consciousness, emotions cannot (we are always feeling something, however low level). It follows that clearly chemicals, forming the basis as they do of brain function, must also form the building blocks of consciousness.

How strange then, that up until now, the silent sector of the brain research community has been the neurochemists and the neuropharmacologists.

This book is now set to buck the trend. Starting with a general introduction to brain chemistry, the reader can take a journey through normal brain processes, into the world of drug-induced changes in consciousness, and finally into the chilling world of dysfunctions in consciousness. Subjects covered are truly comprehensive and of such an astonishing range, that even the dedicated brain specialist will be able to learn something, as well as the non-specialist, and gain a wonderful overview of how consciousness might take place within the brain. The Hard Problem, of course, remains unsolved. But it is only by a truly scientific approach, such as found in these pages, that by building on what we know, we will be able to make any progress at all.

Preface

Just over 10 years ago the British psychologist, Stuart Sutherland stated (in the Oxford Dictionary of Psychology) that consciousness was impossible to define, that its function or even why it evolved is unknown, and that nothing of any value had ever been written about it.

In a recent major text, *The New Cognitive Neurosciences* (2000), Christof Koch and Francis Crick maintain that "precise definitions of consciousness are premature" but suggest "the most promising empirical approach is to discover the neuronal correlates of consciousness". Publications on possible neural correlates of consciousness (NCC) have appeared in increasing numbers during the 1990's—the decade of the brain. Arguments in favour of the relative importance of brain areas such as the cerebral cortex, brainstem reticular activating system or particular thalamic nuclei have been advanced. PET imaging has highlighted blood flow increases in some regions (e.g. anterior cingulate and temporal cortex) and decreases in others (e.g. posterior cingulate and pre-frontal cortex). Proposed neurophysiological correlates have evolved from generalised EEG desynchronization (such as in waking and REM sleep) to specific high frequency (40 Hz) synchronised oscillations which distinguish mental activities with, as opposed to without, conscious awareness. Increasingly articles on the potential importance of specific neurotransmitter systems such as acetylcholine and 5-HT have begun to appear.

In keeping with these developments this book does not seek to explain, or even to define, consciousness. Instead, we have gathered together some of the rapidly accruing information on neurochemical correlates of well recognised states and alterations of consciousness. These include natural functions such as attention, memory, motivation, sleep and dreaming. Changes induced by drugs and by pathological states add further important information based on the premise that mechanisms associated with disrupting or abolishing consciousness will help to identify those underpinning normal conscious awareness.

We start with the premise that conscious awareness is a functional property of the human brain and that its material basis can be illuminated by current neurobiological concepts. The brain contains an array of neuronal networks, the incredible complexity of which limits our understanding of the mecha-

nisms by which cerebral activity gives rise to consciousness. Each of 50 to 100 billion neurons in the human brain connects with over ten thousand others, changing activity as often as 200 times a second. Amidst these dynamic patterns of activated and deactivated neurons, consciousness emerges as a transient awareness of only a minute proportion.

Abstract models of neural networks (based on the properties of individual neurons) show some characteristics, such as learning, similar to those associated with the human brain. These models demonstrate the importance of neurone-to-neurone connections and suggest that consciousness is generated as a result of synchronised activity in relevant, connected, neural networks. In the brain, neurons link largely via synaptic junctions between axonal terminals and dendritic spines. This communication is mediated by chemical neurotransmitters which are therefore central to our understanding of the mechanisms which support consciousness. Yet little has been written of the neurochemical mediators of distributed neural function and their relationship to various conscious states. This book is devoted to filling that junctional gap, enlisting authors who are psychologists, pharmacologists, psychiatrists and neurochemists to consider links between transmitters and consciousness from their particular viewpoint. While the contents of the book are not comprehensive and in places controversial, it aims to add neurotransmitter systems to the growing number of NCC that will influence future understanding of potential mechanisms of consciousness—considered by some to be the next great scientific frontier. For the reader who succeeds in reaching the end of the book there is an 'envoi' or afterword, in which we consider how the different contributions have succeeded in taking forward the case for particular transmitters as new NCC contenders.

Elaine Perry, Heather Ashton, Allan Young
Newcastle upon Tyne

Neurotransmitter Systems

Neurotransmitter networks

Elaine Perry and Allan Young

1. Introduction

This first chapter sets the scene for subsequent exploration of potential transmitter correlates of consciousness by introducing the principal neurotransmitters systems in the brain. In 1921 the German physiologist Otto Loewi dreamed a dream that inspired him to devise the original experiment in which the chemical nature of neurotransmission was discovered (Byron et al., 1993). Coincidentally the transmitter involved was acetylcholine, which is now thought, as a result of activation of brainstem cholinergic neurons, to trigger REM sleep and promote dreaming (Chapters 7 and 8). It was later established that neurons link via synaptic junctions (Fig. 1) and that communication is mediated by the relay of chemical signals interacting with specific receptors. These receptors initiate both rapid (ion channel linked) and slow (G-protein coupled, metabotropic) neuronal responses with time-scales of response in the millisecond and second range (respectively). Responses in the recipient neuron include immediate changes in cation influx and stimulation of intracellular second messengers, and in the longer-term alterations in gene transcription and architectural changes in synaptic and dendritic morphology (Fig. 1).

Since the discovery of acetylcholine, over 50 other neurotransmitters or neuromodulators have been identified in the brain. The principal excitatory and inhibitory transmitters, glutamate and GABA, are widely distributed in neurons throughout the brain. By contrast modulatory transmitters originate in discrete nuclei with widespread connections to many brain areas, providing an integrative or "binding" potential for conscious awareness. These multiple pathways, utilising monoamines, acetylcholine, neuropeptides and other chemicals as transmitters, modulate various brain functions such as arousal, attention, mood, learning, memory, motivation, sleep and dreaming. Often
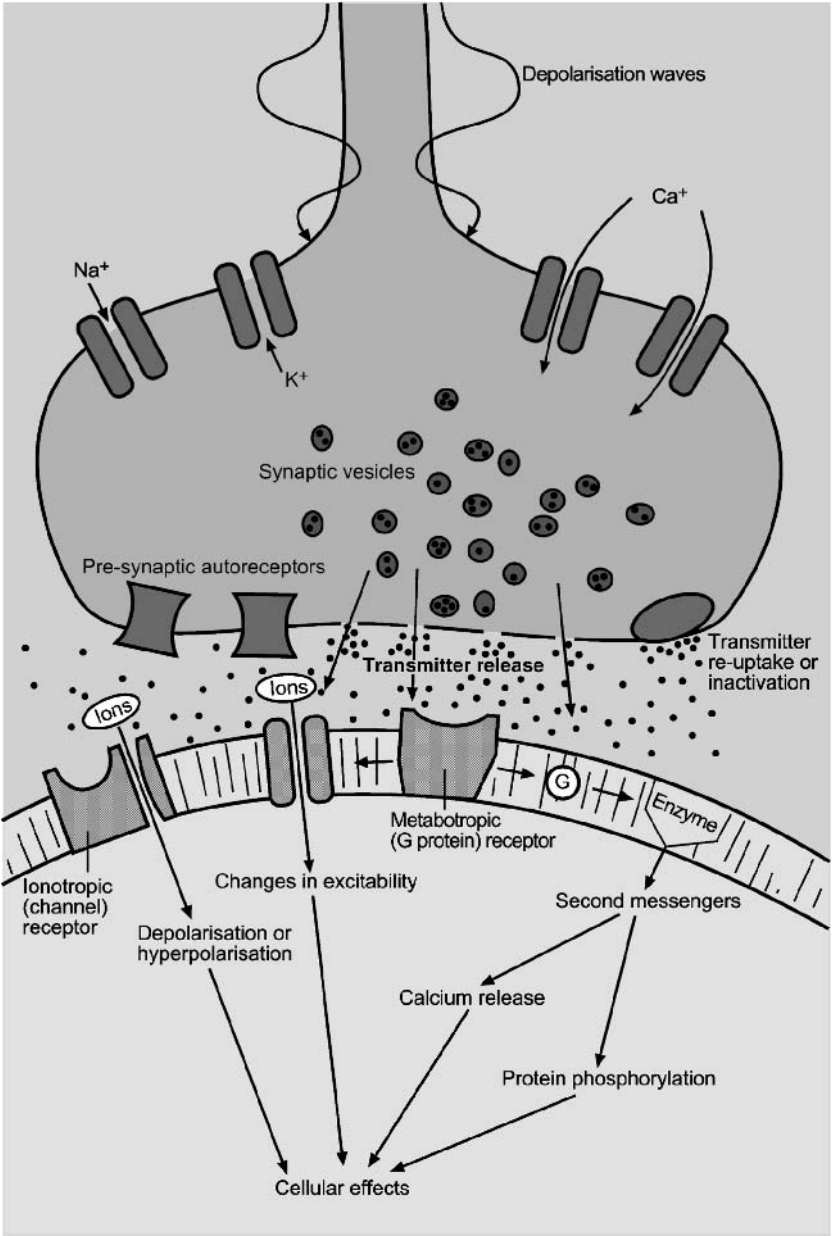
Figure 1. Schematic diagram of a synaptic junction demonstrating the principle of chemical neurotransmission.

with overlapping functions, these modulatory systems influence the activity of ubiquitous executive glutamate and GABA neurons.

A global view of consciousness is that it is generated throughout the entire brain, as a result of synchronisation of relevant neural networks. Specific systems or regions—for example the cerebral cortex, brainstem reticular formation and thalamic nuclei—may be key anatomical integrators. Areas with the most widespread interconnections are pivotal, and on this basis the cortex and thalamus are more relevant than cerebellum and striatum for example. Frontal cortex for example connects with every other brain region, both in terms of input and output, with 80% of such connections accounted for by cortico-cortical connections. Thalamic intralaminar nuclei are, in conjunction with the reticular nucleus, reciprocally connected to all cortical areas. By contrast the cerebellum has very few output pathways and striatal-cortical input is (via the thalamus) confined to frontal lobe.

Characteristics of transmitter systems likely to provide network integration potentially generating consciousness include the following:

1. Neuronal activity correlating with natural variations in conscious awareness from states of wakefulness, dreaming and non-dreaming sleep, and also with effects of drugs and diseases which affect consciousness.
2. Activity that leads to network selection and integration (e.g. 40 Hz synchronicity), distinct from the vast parallel array of neuronal networks involved in non-conscious processing.
3. Originating in a discrete locus or loci of co-ordinated neurons with either direct or indirect (e.g. via GABA interneurons) reciprocal connections with such key areas as cortex, thalamus and brainstem reticular activating system.
4. Modulatory neurophysiological effects that are both tonic (setting a level of consciousness) and phasic (responding to novel or relevant stimuli).

2. Glutamate and GABA executive transmitter systems

These amino acid transmitters are predominant, accounting for most of the fast synaptic transmission in the brain. Together they occur in 70–80% of cerebral neurons. The concentration of GABA is for example up to 1000 times greater than that of other transmitters like acetylcholine or dopamine.

GABA is the principal inhibitory transmitter in the brain exerting a direct depressant effect on neurons by hyperpolarization and reducing release

of other transmitters. GABA function is generally increased during sleep and decreased in hyperarousal states such as anxiety. Neurons containing GABA are relatively small, usually intrinsic and widely distributed, especially in more rostral regions—cerebral cortex, striatum, hypothalamus, septum and thalamus for example, compared to cerebellar cortex and spinal cord (Parnavelas, 1990). In the cerebral cortex, GABA neurons form a prominent band in layer IV which is the principal target of thalamic projections. Visual cortex, the dominant sensory input area, has 50% more GABA neurons than other cortical areas—indicative of the importance of neuronal inhibition in the generation of coherent neural networks. GABA neurons are particularly implicated in plasticity—alterations in the structure of synaptic junctions, dendrites and dendritic spines in response to functional changes (Guidotti et al., 2000). A variety of $GABA_A$ ionotropic receptors are concentrated in cortex and cerebellum, $GABA_B$ metabotropic receptors being less prevalent.

Larger glutamate neurons with much longer projections convey information across greater distances. Glutamate is the principal excitatory transmitter in the brain with receptors concentrated in key areas such as hippocampus and neocortex. Projection or relay pathways are predominantly cortical in origin and include: cortico-cortical; corticostriatal (from entire neocortex, ipsilaterally, to caudate and putamen); corticothalamic (cortex to thalamic nuclei, ipsilateral); prefrontal cortex to substantia nigra; sensorimotor cortex to red nucleus and spinal cord; corticopontine; perforant pathway (entorhinal to hippocampus); hippocampal to septal nuclei; and cerebellar cortex to the inferior olive. In the cortex, glutamate occurs in pyramidal neurons in layers IV to VI and is concentrated in layers II and III—the latter being the origin of many cortico-cortical and cortico-fugal projections (Parnavelas, 1990). Ionotropic glutamate receptors include NMDA and AMPA subtypes which are concentrated in cortex and striatum, but lower in cerebellum, and the kainate subtype which has a complementary distribution. NMDA receptors are unique in depending on simultaneous pre synaptic release of glutamate and post synaptic depolarisation (removing inhibitory magnesium ions).

A close balance of activity between GABA and glutamate controls the general level of brain activation. Together GABA and glutamate interactions are likely to underpin automatic cerebral activities, processed in parallel and at great speed, of which there is no conscious awareness. Glutamate is likely to be important in the interface between modal and reciprocal transmission, and its role in learning and memory, and in the classical model of learning—long-term potentiation is considered in Chapter 4.

3.   Modulatory systems

Superimposed on these ubiquitous primary control mechanisms are a complex series of modulatory transmitter systems. These originate in discrete subcortical nuclei and simultaneously influence neurons in diverse projection areas which carry the relevant receptor. Such transmitters include acetylcholine which has been specifically implicated in the process of conscious awareness (Woolf, 1997; Perry et al., 1999; see also Chapter 2) since activity in select cholinergic neurons correlates with levels of consciousness varying between waking, dreaming and non dreaming sleep (Chapters 6–8). In addition the monoamines noradrenaline, adrenaline, dopamine, serotonin and histamine, have anatomical features in common. Neuronal cell bodies are generally confined to small midbrain or brainstem nuclei. All of these monoaminergic except dopaminergic neurons are reduced in activity during sleep including both non-REM and REM sleep (Chapters 6–8). This indicates that consciousness may not primarily depend on these transmitters, although they are likely to contribute to various alterations in consciousness.

These modulatory transmitters are released from both synaptic terminals and axonal varicosities, providing not only 'point to point' (pre- to postsynaptic) but also extending integrative potential, 'volume control'. There are also a larger number of modulatory neuropeptide systems including for example the opioid peptides, together with more recently discovered endogenous cannabinoids, adenosine and nitric oxide transmitters, that are likely to be relevant. In relation to receptors for these modulatory transmitters cholinergic receptors are relatively unique in being both ionotropic (nicotinic) and metabotropic (muscarinic); almost all the other modulatory transmitter receptors are metabotropic.

3.1   Acetylcholine

Cholinergic systems are more numerous than the other modulatory systems and distributed in a wide range of brain areas. Of particular interest in relation to consciousness, discrete nuclei situated rostrally and caudally provide both widely divergent and, in some key areas such as frontal and occipital cortex and thalamus, also convergent projections (Fig. 2). In the basal forebrain, septal neurons innervate hippocampus, cingulate and retrosplenial cortex; diagonal band neurons innervate entorhinal and olfactory cortex; and the nucleus of Meynert innervates the remainder of the cortex, amygdala and select thalamic nuclei. Cholinergic terminals in the cortex are concentrated in superficial layers
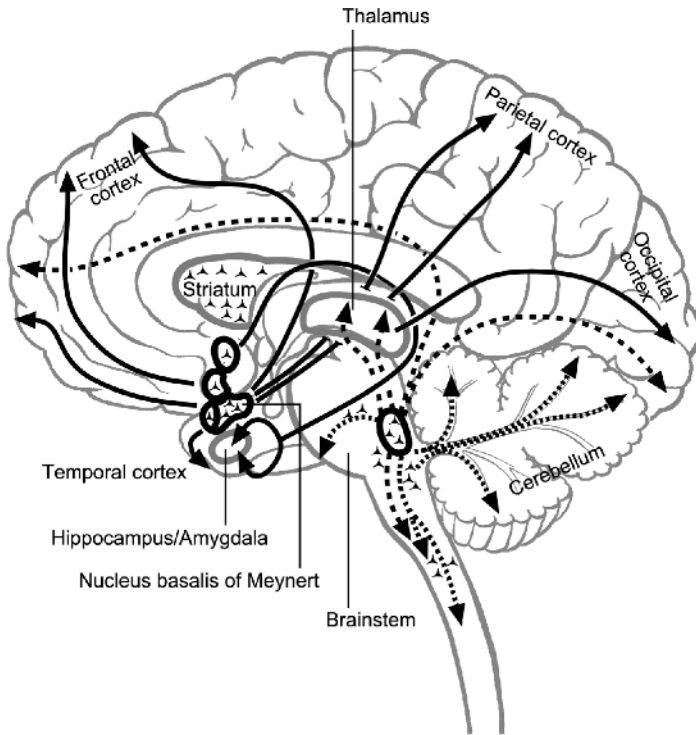
Figure 2. The cholinergic system in the human brain. The two principal pathways projecting from discrete nuclei are shown as basal forebrain (continuous lines) and pedunculopontine/dorsal tegmental (dotted lines).

I and II and also layers IV. Activity of the basal forebrain neurons is necessary for maintaining wakefulness and, functions of these and brainstem cholinergic nuclei include arousal, selective attention and REM sleep (Ch. 2).

According to Mesulam et al. (1995) the size of nucleus basalis cholinergic projections to the cortex indicates that "this pathway is likely to constitute the single most substantial regulatory afferent system of the cerebral cortex." Based on the maintenance of cortical activation during REM sleep in the absence of monoaminergic (e.g. noradrenergic and 5-HT) activity but continued firing of cholinergic nucleus basalis neurons, Buzsaki et al. (1988) concluded that "the ascending cholinergic system alone is capable of keeping the neocortex in its operative mode." The consensus view on the role of these cholinergic projections is that they control selective attention. Since Delacour (1995) has speculated that selective attention and consciousness overlap, and Baars et al.

(1998) has highlighted the importance of selective attention in the "theater" metaphor of consciousness, the two processes may share a common neural basis. Basal forebrain cholinergic neurons also project to select thalamic nuclei, including the reticular nucleus, which with topographical cortical input is also implicated in selective attention.

85–95% of brainstem afferents to most thalamic nuclei, including both specific relay and reticular nuclei, originate in the region of the rostral midbrain core where cholinergic pedunculopontine and lateral dorsal tegmental nuclei are maximally developed. Amongst thalamic nuclei the intralaminar, specifically implicated in conscious awareness [Bogen et al., 1995], receive the highest density of brainstem cholinergic afferents. These thalamic inputs are excitatory both via direct, early nicotinic and slower muscarinic depolarization and via hyperpolarisation of GABAergic reticular neurons. Co-activation of rostrally projecting brainstem and forebrain cholinergic neurons, such as occurs in both wakefulness and REM sleep, provides the thalamus and with an integrative modulation of that could represent a component mechanism of conscious awareness.

Electrophysiologically, acetylcholine is involved in excitatory, phasic neurotransmission. The basal forebrain cholinergic system has been implicated in the generation of an attending potential known as the P_{300} thought by some to be a component of conscious awareness (reviewed Perry et al., 1999), although this is controversial. Investigation in human subjects have demonstrated P_{300} latency increases and amplitude reductions with the administration of scopolamine (a muscarinic antagonist), reversed by physostigmine. These findings are consistent with animal studies which have shown physostigmine alone increases the P_{300} amplitude. Lesions of cholinergic basal forebrain neurons result in P_{300} latency delay and amplitude reductions. This effect is reversed with vagal (cholinergic neuron enriched) implants, restoring P_{300} characteristics which correlate with the restoration of cortical levels of the cholinergic enzyme choline acetyltransferase. One of the most compelling arguments in favour of a primary role for forebrain acetylcholine in conscious awareness is that unlike other transmitter systems its release in the cortex correlates with the level of awareness: high during waking, low during slow wave sleep and increased during REM sleep (reviewed Perry and Piggott, 2000).

Other cholinergic pathways in the brain include a network of intrinsic neurons in the striatum, and also various nuclei in the lower brain stem which project to the cerebellum are the origins of the cranial nerves. Striatal cholinergic neurons project mainly to spiny neurons which are the principal locus for the relay of cortical information flow through the basal ganglia (Calabresi et al.,

2000). Such pathways are more likely involved in sub-conscious information processing.

The correlation between basal forebrain cholinergic activity and variations in conscious awareness between waking, sleep and dreaming suggests this transmitter system is centrally involved in consciousness. Interestingly cholinergic blockade improves performance in tasks which depend on implicit cognition (Callaway and Band, 1958). If cholinergic rostral projecting neurons are centrally involved in integrating conscious awareness, the question of whether any particular receptor subtype is involved arises. In the cortex muscarinic and nicotinic receptors are widely distributed on pyramidal and non pyramidal neurons. Muscarinic metabotropic receptors are concentrated in cortex and striatum, the predominant subtypes M1 and M4 being found to the greatest extent in these regions. M3 is predominant in the thalamus and M2 in cerebellum. Nicotinic ionotropic receptor subtype distributions are still being established (Court et al., 2001). The high affinity receptor (predominantly $\alpha_4\beta_2$) is widely distributed and concentrated in thalamus (particularly lateral geniculate nucleus), midbrain (e.g. substantia nigra), striatum and limbic cortex (e.g. subiculum and entorhinal cortex). The low affinity nicotinic receptor (α_7) is found in hippocampus, substantia nigra and most strikingly in the reticular nucleus of the thalamus. The rapid desensitization of nicotinic receptors could be relevant to the rapid variance in neural activity that is thought to be required to support and sustain conscious perception.

In many cortical neurons acetylcholine is not directly excitatory, but enhances neuronal responses to glutamate. Reinforcing the actions of executive transmitters such as glutamate and GABA, acetylcholine could increase competition between excitatory and inhibitory states so restricting neuronal numbers depolarising at any one time to those most relevant to the immediate external or internal environment. It may be relevant that in rat brain cortical activation reduces intralaminar inhibition through nicotinic receptors and promotes intracolumnar inhibition through muscarinic receptors (Xiang et al., 1998), so changing the direction of information flow within cortical circuits.

3.2 Dopamine

In contrast to acetylcholine, dopamine has both excitatory (D1) and inhibitory (D2 and D3) receptors. Dopaminergic neurons occur in two closely connected groups: A10—ventral tegmental area (VTA), and A9—substantia nigra, pars compacta (Fig. 3). While substantia nigra neurons project to the striatum, VTA
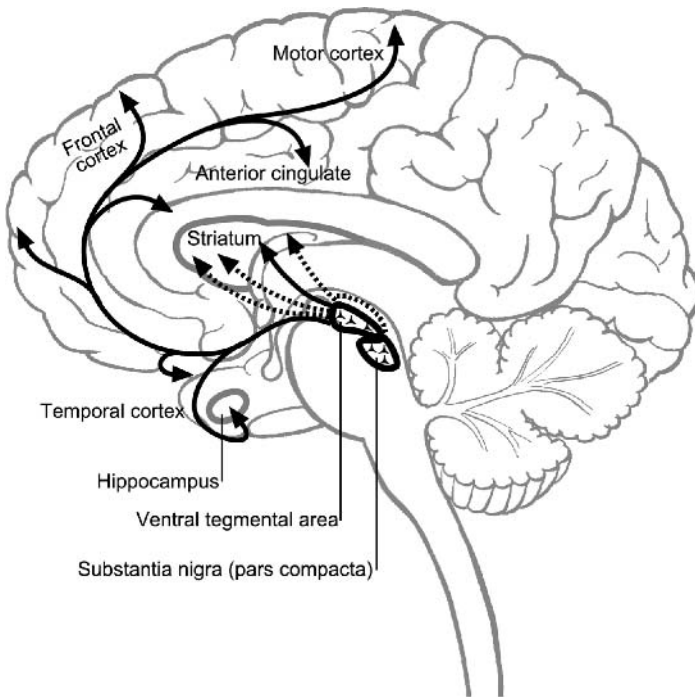
Figure 3. The dopaminergic system in the human brain—the two principal pathways projecting from discrete nuclei are shown as ventral tegmental (continuous line) and substantia nigra pass compacta (dotted lines).

neurons project to limbic cortex and amygdala. VTA neurons fire continuously during all phases of the sleep/wake cycle (Chapters 7 and 8).

Dopamine transporters in the cortex are concentrated in cingulate and medial prefrontal regions (Oliver et al., 2000). While cholinergic and noradrenergic systems are said to be involved in 'low level' aspects of attention (e.g. attentional orienting) (see also Chapter 4), the dopaminergic system contributes to motivated behaviours (Chapter 5), and is said to be associated with more 'executive' aspects of attention such as attentional set—shifting or working memory (Coull, 1998). It has recently been suggested that dopamine rather than signalling pleasure may function to highlight significant stimuli (Wickelgren, 1997).

While in the non primate brain dopaminergic projections to the cerebral cortex are restricted to only a few areas (prefrontal, anterior cingulate, entorhinal and perirhinal together with the amygdala), in man and other primates, the cortical innervation is much more widespread and highly differentiated with

respect to laminar and regional patterns (Berger et al., 1991). Primary motor cortex is the most densely innervated followed by somatosensory and other sensory areas—these being denser that the respective cortical association areas.

In addition to the A9 and A10 cell groups, there are other dopaminergic nuclei in the lateral tegmental area just caudal to the substantia nigra which may be less relevant to consciousness. These innervate the nucleus accumbens, caudal hypothalamus, infundibular nucleus, zona incerta, and in rostral hypothalamus project to septal, hypophyseal and spinal cord regions. There are also intrinsic dopaminergic neurons in the olfactory bulb, and it has recently been reported that there are small numbers of dopaminergic (dopamine transporter positive) neurons in the caudate nucleus (Porritt et al., 2000).

Dopamine receptors include at least 4 subtypes which are concentrated in the striatum where D1 and D2 are evenly distributed and D3 is concentrated in the limbic portion, nucleus accumbens (Herroelen et al., 1994). D2 but not D1 receptors also occur throughout the cerebral cortex particularly temporal lobe, and D3 receptors are also present in lower densities in hippocampus and amygdala. D3 receptors are localised in several thalamic nuclei including the lateral geniculate, mediodorsal and anteroventral.

3.3   Norepinephrine

Norepinephrine or noradrenaline, and epinephrine or adrenaline are the prototypic signals mediating increased activity in response to arousal or stressful stimuli. Central noradrenergic pathways control both cerebral and sympathetic activities. Neurons which synthesise noradrenaline are restricted to the pontine and medullary tegmental regions (Fig. 4). Most are situated in the locus coeruleus from which two major ascending fibre systems arise. Most areas throughout the brain receive an input from both ipsi and contralateral locus coeruleus neurons which are said to be unsurpassed in ubiquity and divergence of their projections, although similar statements are made about raphé neurons. The dorsal noradrenergic bundle innervates almost all thalamic nuclei, the hypothalamus, amygdala, septal nuclei, the hippocampal formation and entire neo and archi cortex (including cingulate and entorhinal cortex). Noradrenergic innervation of the cortex was originally considered to be more diffuse and uniform than for any other of the cortical input systems. This is now disputed, as distinct regional and cortical laminar patterns of innervation have been described. Such patterns are most pronounced in primate including human cerebral cortex, where innervation of sensory motor areas is most dense. Via collateral branches many individual locus coeruleus neurons simul-
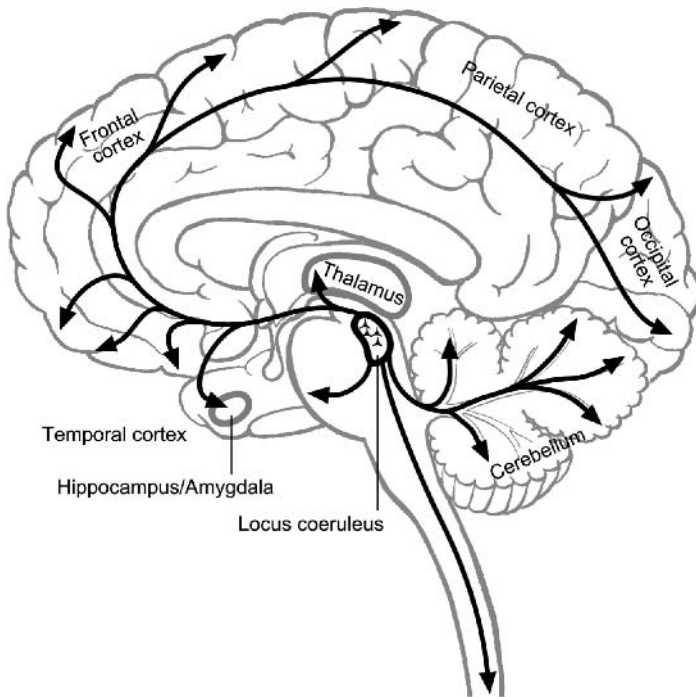
Figure 4. The principal noradrenergic system in the human brain.

taneously innervate widely different regions of the nervous system. The nora-
drenaline transporter, assessed using nisoxetine binding, is concentrated in the
locus coeruleus, anteroventral nucleus of the thalamus and hypothalamus; high
in the paraventricular nucleus of the thalamus and hippocampus, and moder-
ate in the dorsal and medial raphe nuclei and amygdala (Oliver et al., 2000).
Noradrenergic receptors include α_1, α_2 and β-adrenergic each of which exists
as three subtypes. The β_1 subtype predominates in the cerebral cortex and β_2
in the cerebellum.

Although other noradrenergic cell groups exist in the medulla oblongata,
subependyma, pontine tegmentum and lateral reticular formation, the main
body of the locus coeruleus, referred to as the central equivalent of a sym-
pathetic ganglion, is thought to function as a central 'alarm' system. The lo-
cus coeruleus is widely implicated in vigilance and attention, and neurons ex-
hibit phasic or tonic modes of activity which correspond to, respectively to
increased or decreased performance in visual discrimination tasks in monkey
(Aston-Jones et al., 1999). It has been suggested that the phasic mode promotes

focussed or selective attention, whereas the tonic mode relates to high behavioural flexibility or scanning attentiveness. Dorsal projections to thalamus and cortex would appear to be the most relevant to conscious awareness.

3.4 Serotonin

Even more expansive than noradrenergic projections are those originating from the brainstem raphé nuclei which contain the indolamine transmitter serotonin or 5-HT (Fig. 5). These neurons have highly branched fibres which innervate virtually the entire central nervous system. 9 sub-groups (B1–B9) of serotonergic neurons within the raphé have been identified. 5-HT neurons are frequently mingled with other neuron types containing dopamine, noradrenaline, GABA and several peptides. The raphé nuclei have accordingly been described as a multiple transmitter complex. This concept is further supported by the coexistence of peptides such as substance P and TRH with serotonin.

Figure 5. Serotonergic systems in the human brain with projections to the cerebral cortex from the dorsal raphé nucleus (continuous line) and from the median raphé nucleus (dotted line). Projections from more posterior nuclei also as continuous lines.

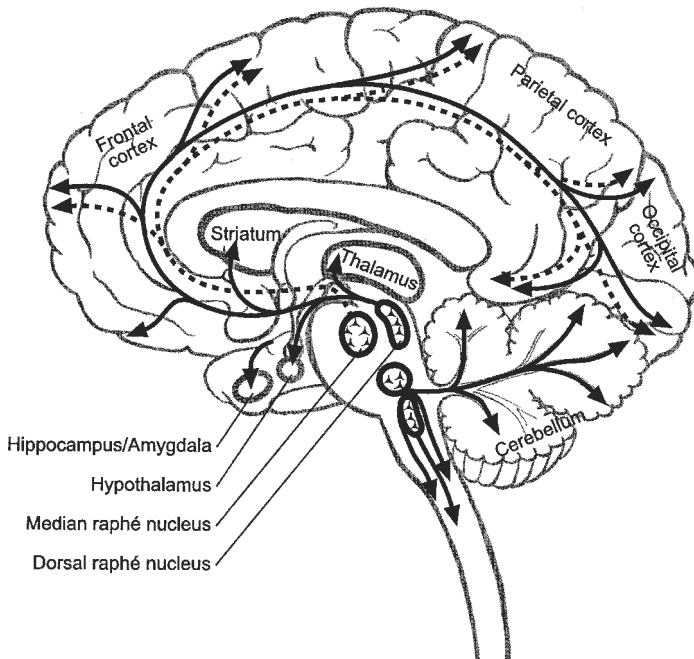In the human brain the most prominent nucleus is the dorsal raphé. Arising from groups B6–B8, including dorsalis and centralis superior nuclei, is the large ventral ascending serotonergic pathway which innervates the interpeduncular nucleus, substantia nigra, ventral tegmentum, thalamus and hypothalamus. A lateral contingent proceeds to the amygdala, striatum and both lateral and caudal neocortex, whilst the ventral tract innervates hippocampus, rostral and lateral neocortex and also innervates thalamus and amygdala. Other serotonergic projections include: the dorsal ascending pathway which eventually joins the ventral path; projections to rhombencephalic centres (including locus coeruleus and dorsal tegmentum); and a cerebellar pathway emerging from all the raphé nuclei and bulbospinal path.

The entire neocortex receives a serotonergic innervation which, as with dopamine and noradrenaline, demonstrates a regional and laminar distribution in primate but not rodent brain. The cortical expansion in primate may account for the fact that the percentage of serotonergic fibres in the medial forebrain bundle is 25% compared with less than 1% in the rat. The two parallel 5-HT systems from dorsal and medial raphé overlap in most areas which thus receive dual 5-HT innervation. Fine fibres originate from the dorsal raphé and course, beaded fibres from the median raphé or varicose. The former are preferentially associated with 5-HT_2 receptors and the latter with pre-synaptic 5-HT_{1A} receptors, indicating different functional roles for the 2 pathways. In primate brain, visual cortex is the most densely innervated of all neocortical areas although frontal and cingulate areas are also high. In most areas the concentration of 5-HT decreases from upper to lower cortical layers. The thalamus is apparently a major site of serotonergic transmission in man (Smith, 1999). Radiolabelled selective serotonin reuptake inhibitors (SSRIs) detected using PET or SPECT are particularly dense in dorsomedial and adjacent thalamic nuclei.

Serotonergic dendrites and axons are often found in contact with blood vessels raising the question of whether serotonin may be particularly important in volume control neurotransmission. 5-HT is released into the ventricular csf through which it exerts a hormonal-like influence on receptors distant from the axonal terminals. Together with the intermingling of cell bodies with other transmitters, and extremely widespread projection of fibres this suggests a major role for 5-HT in neuronal integration. Since 5-HT is primarily an inhibitory transmitter, an integrative role in conscious awareness could involve selective suppression of neuronal activity, an essential component of neuronal network function. It has been proposed that 5-HT functions as a general inhibitor of behavioural responding. During REM sleep, 5-HT neurons are practically silent

and hallucinatory images of dreaming may relate to the loss of cortical 5-HT induced inhibition (Chapter 7).

How the 14 or more 5-HT receptor subtypes (Verge and Calas, 2000) contribute to network neuromodulation is unknown. $5HT_{1A}$ receptors are widely distributed, concentrated in limbic areas (e.g., hippocampus and amygdala), with high densities in upper layers (I and II) of the cerebral cortex and also in raphé nuclei, and lower levels in striatum and thalamus. This autoreceptor occurs on the soma and dendrites of 5-HT neurons, exerting a negative feedback influence on their activity and desensitizing on prolonged receptor interaction (Blier et al., 1998). Basal ganglia and to a lesser extent hippocampus but not thalamus have $5HT_{1B}$ receptors, and the $5HT_{1D}$ receptor subtype is also evident in basal ganglia and to a lesser extent cortex and amygdala. $5HT_2$ or $5HT_{2A}$ receptors, specifically implicated in hallucinogenesis (Chapters 12 and 13), are concentrated in cerebral cortex, particularly in pyramidal (layer III) neurons of frontal cortex and also granule cells (layer IV) of striate (visual) cortex (layer IV). 5HT3 receptors are present at low densities in cortex with highest densities in medulla and spinal cord.

While 5-HT is associated with a spectrum of behaviours such as mood, anxiogenesis and sleep (Lucki, 1998), it is possible on the basis of characteristic alterations in consciousness associated with indoleamine drugs (Chapters 12 and 13), that it is also involved in generating self consciousness.

3.5 Histamine

A fifth member of the monoamine transmitter group is histamine. Neurons positive for histidine decarboxylase are confined to caudal hypothalamus (tuberomammillary nuclei) and project to many areas including cerebral cortex (particularly layer I), basal forebrain, thalamus and pontomesencephalic tegmentum. It is thought that, like noradrenergic neurons, histamine neurons function as a homogeneous group, simultaneously releasing transmitter throughout the brain. These act as a regulatory centre for whole brain activity governing a range of functions, including arousal, learning and memory (Passani et al., 2000).

H1 receptors occur throughout the CNS with particularly high densities in the thalamus and hippocampus and are thought to mediate arousal effects of histamine. H2 receptors are concentrated in the striatum, hippocampus and thalamus and H3 receptors in cortex, hippocampus and amygdala. Histamine levels diminish during sleep and H1 antagonists which cross the blood brain

barrier induce sedation. Histamine neurotransmission may thus be involved in controlling the level of consciousness during waking.

3.6 Neuropeptides

Numerous peptides have been identified in neurons throughout the brain with neurophysiological characteristics of the classical transmitters described above, but occurring at much lower concentrations. These small peptides interact with specific receptors, but do not have rapid reuptake systems for their inactivation being instead hydrolysed by broad spectrum peptidase enzymes. Neuropeptide action is thus longer lasting than most classical transmitters and probably, by virtue of cerebrovascular transport, much more wide ranging across different brain areas. Many neuropeptides (e.g. somatostatin, MSH, neuropeptide Y, TRH, galanin, substance P, CCK, CRH, VIP, neurotensin) are co-localised in specific hypothalamic nuclei (Lantos et al., 1995) and are involved in the regulation of basic functions as food, water and salt intake and sexual activity. Others, such as the endogenous opiates (endorphins, dynorphins and enkephalins) are primarily concerned with stress responses triggered by perception of pleasure or pain. It would be difficult to argue based on localisation and neurophysiology that such neuropeptides are specifically involved in the rapidly transient integration required for conscious awareness. They are therefore considered only briefly below.

Substance P
Substance P exerts a slowly developing and long lasting excitatory effect on neurons. 20% of cell bodies in the dorsal root ganglia contain this peptide and, in projecting to the dorsal horn of the spinal cord, are thought to convey information concerning a variety of epidermal—particularly pain, glandular and vascular—activities. Substance P neurons in the brain include: cell bodies in the brainstem reticular formation; habenular nuclei projecting to the dorsal raphé for example; medium sized neurons in caudate and putamen which project to the substantia nigra pars reticulata which contains the highest concentration of any brain area; cortex (most commonly layers V or VI); amygdala, and hypothalamus. Substance P coexists with acetylcholine in a proportion of the cholinergic dorsal tegmental pathway. Substance P antagonists have excited interest recently as potential antidepressants (Hokfelt et al., 2001).

Vasoactive intestinal peptide
The highest concentration of vasoactive intestinal peptide (VIP) is in the cerebral cortex where 1% of the neurons are VIP-positive. The role of VIP in stimulating glycogen hydrolysis, lipolysis, insulin secretion and inhibition of gastric secretion may well be reflected in a nutritional function of the peptide in the CNS, where it has been suggested that it may regulate cortical energy metabolism. Most of the cortical neurons are concentrated in the middle layers are intrinsic or local circuit although some project trans-callosally. Small numbers of VIP neurons in caudate and putamen provide numerous fibres in the globus pallidus and there are also scattered cells in such areas as the amygdala and olfactory bulb.

Cholecystokinin
Cholecystokin (CCK) is also most widely distributed in the cortex where it is thought to control appetite and satiety. Neurons in the cortex, mainly in layers I–III, are non pyramidal with fibres terminating in layer VI. The highest brain level is found in the striatum, including nucleus accumbens where fibres originate from the ventral tegmental area. Here a subpopulation of the A10 dopaminergic neurons contain CCK. There are also CCK neuronal clusters in the septal nuclei, hypothalamic nuclei, around the raphé nuclei, and in the mesencephalic grey matter which is an effective stimulation site for analgesia—CCK is a potent analgesic (but also strongly anxiogenic).

Neurotensin
Neurons containing neurotensin (NT) are concentrated in the hypothalamus and project widely, including to the lower layers of the cerebral cortex. NT containing cells also occur many brain areas including striatum, amygdala, diagonal band of Broca, raphé, and, as with CCK, also in the ventral tegmental area. Receptors are localised in basal forebrain cholinergic neurons, dopaminergic nuclei and hypothalamus. NT has several actions in common with neuroleptic drugs e.g. antagonists block antipsychotic drug effects in models of schizophrenia, suggesting it may act in the mesolimbic dopaminergic system as an endogenous neuroleptic (Kinkead et al., 1999). The peptide also influences sensitivity to pain; analgesic effects are induced by injections of the peptide into the central amygdaloid nucleus.

Hypothalamic peptides
A group of peptides including corticotropin-releasing factor (CRF), luteinizing hormone–releasing hormone (LH–RH), somatostatin and thyrotropic re-

leasing hormone (TRH) are synthesised in the hypothalamus, from where via the pituitary they control a range of physiological functions. CRF neurons also occur in the amygdala, reticular formation, dorsal raphé, locus coeruleus, thalamus, basal forebrain, hippocampus and superficial layers of the cerebral cortex. Intraventricular injections of CRF are associated with anxiogenic-like effects, increasing measures of anxiety, behavioural activation and changes in autonomic function. CRF may have a reciprocal role with neuropeptide Y in converting stressful stimuli into appropriate behavioural and physiological responses. LHRH containing neurons are clustered in and around the hypothalamic nuclei and while this peptide functions primarily to stimulate secretion of luteinizing hormone and follicle stimulating hormone with subsequent effects on reproductive or sexual behaviour, the possibility that certain groups relate to other CNS functions has not been excluded.

Somatostatin inhibits secretion of growth hormone and other hormones such as prolactin from the anterior pituitary and is widely distributed in the brain in interneurons and projection pathways. All parts of the cortex contain local circuit somatostatin positive neurons, concentrated in layers V and VI, as does the amygdala and striatum. The nucleus accumbens and adjacent ventral putamen and caudate—designated limbic striatum—have particularly high concentrations of fibres. By contrast, TRH which regulates release of thyroid stimulating hormone and prolactin by the pituitary is generally confined to nuclei in and around the hypothalamus.

Endorphins/enkephalins

Endorphins and enkephalins act as the endogenous ligands for opiate receptors. A common large precursor, pro-opiomelanocortin gives rise to β-lipotropin which is cleaved to β-endorphin, an extremely potent opioid agonist. Endorphins occur particularly in hypothalamic neurons, projecting widely to such areas as amygdala, septum and brainstem. In behavioural terms, they are involved in regulating responses to stress, and stimulating the release of other hormones such as growth hormone and prolactin. The reduction in responsiveness to pain associated with stress is thought to involve endorphin release and interaction with periaqueductal grey, other brainstem and spinal cord regions which gate sensory information from the periphery.

The enkephalins, derived from pro-enkephalin, are distributed much more widely in the CNS both in local circuit neurons and projection neurons, a distribution generally paralleling to that of the opiate receptors. Leu-enkephalin predominates over Met-enkephalin and both peptides are inhibitory. Enkephalin containing neurons are sparsely distributed in upper lay-

ers of the neocortex but are more concentrated in limbic cortex (entorhinal and cingulate). The central nucleus of the amygdaloid complex is densely populated. Enkephalin neurons are also present in several centres which modulate conduction of nociceptive impulses—griseum centrale mesencephali, reticular formation and substantia gelatinosa of the spinal trigeminal nucleus and spinal dorsal horn. These interneurons form axon-axonic inhibitory synapses with pain afferents. The periaqueductal grey, which generates potent analgesia in response to electrical stimulation or opiate injection, contains a high density of opiate receptors.

A third family of endogenous opiates is the dynorphins. Dynorphins are extraordinary potent opiate agonists and selective for the opiate receptor subtype kappa. Dynorphin occurs throughout the CNS, most concentrated in the pituitary-hypothalamus and also high in substantia nigra, amygdala, striatum, hippocampus and spinal cord areas. In these areas, and to a lesser extent cortex, neuronal cell bodies are positive with projections within and outside the local area. Neuroendocrine and sensory functions are thought to be governed by dynorphin.

In the hippocampus, enkephalins facilitate and dynorphins inhibit long-term potentiation (Simmons and Chavkin, 1996). Consistent with the role of these peptides in nociception, electroacupuncture selectively induces release of enkephalins and dynorphins in both human and experimental animals (Ulett et al., 1998).

Neuropeptide Y
One of the more recently identified peptides, neuropeptide Y, is extensively distributed with high densities of cell bodies and terminals in the amygdala. There are complex patterns of coexistence with other transmitters such as catecholamine, GABA and somatostatin. Although primarily considered in relation vegetative functions, such as stimulating food intake, modulating circadian rhythms and controlling release of hypothalamic hormones including CRF, this peptide has also been implicated in anxiety, depression and behavioural responses to stress.

3.7 Cannabinoids

Analogous to the discovery of the endogenous opiates and opiate receptors, the discovery of cannabinoid receptors in 1988 suggested the presence of endogenous cannabimimetic compounds. In 1992 anandamine—the ethanolamide of arachidonic acid was purified from porcine brain and shown to behave

as a typical cannabimimetic compound. Other endogenous ligands include 2-arachidonylglycerol and other polysaturated N-acylethanolamines (Di Marzo et al., 1999). These are all synthesised by neurons and inactivated by reuptake. Cannabinoid receptors and their endogenous ligands constitute a novel modulatory system that is considered to be involved in nociception, memory, regulation of movement and neuroendocrine function (Fernandez-Ruiz et al., 2000). Anandamine or arachidonyl ethanolamine, an endogenous receptor ligand, provided exogenously does not substitute for delta 9-tetrahydrocannibinol (THC, the psychoactive ingredient of cannabis) with respect to subjective effects (Wiley, 1999). THC interferes with short term memory (Hampson and Deadwyler, 1999). Cannabinoids supress nociception at the level of the thalamus and spinal cord (Walker et al., 1999). CB1 and CB1A receptors are present in mammalian brain at higher levels than most other G-protein coupled receptors and found predominantly in hippocampus, cerebellum and striatum (Breivogel and Childers, 1998). The psychoactive cannabinoids increase the activity of dopaminergic neurons in the ventrotegmental area (Ameri, 1999) which is likely to relate to reinforcement behaviour.

3.8 Purines—adenosine and ATP

Purines such as adenosine and ATP exert a modulatory influence on the CNS by activating G protein coupled receptors: 4 different adenosine receptor subtypes (A1, A2A, A2B and A3) and over 5 ATP (P) receptors. Adenosine is a strong candidate for a sleep inducing factor. The concentration of adenosine is thought to rise during waking until by inhibiting basal forebrain cholinergic neurons it triggers sleep onset (Porkka-Heiskanen, 1999; see also Chapter 6). Systemic administration of adenosine induces sleep and antagonists such as caffeine and theophylline induce wakefulness and vigilance. Adenosine A2A receptors are concentrated in striatum, nucleus accumbens and olfactory tubercles and also present in neurons and microglia in most other brain areas (Moreau & Huber, 1999). There are antagonistic interactions between these and dopamine D2 receptors, the affinity of the latter being reduced by A2A stimulation. Since caffeine is the most widely used 'psychotropic' drug, it could be argued that adenosine receptor modulation is one of the most important modulatory mechanisms of altering the level of consciousness.

Other than adenosine, there are several peptides which induce sleep (e.g., delta sleep inducing peptide). Together with endogenous chemicals interacting with the GABA benzodiazepine receptor site (e.g., β-carbolines) identified in

brain and suggested to be endogenous anxiolytics signals, future discovery of novel transmitter systems can be anticipated.

3.9 Corticosteroid hormones

In addition to these and other CNS neuropeptides, there is also a wide range of corticosteroid and gonadal steroid (testosterone, oestrogen, progesterone) receptors distributed in the brain. The brain is a principal target organ for many steroid hormones, which play a role in the structuring of the developing brain and restructuring of the adult brain. Corticosteroids are thought to alter brain architecture, in particular reducing dendritic arborisation (Young et al., 1999). In addition, steroid hormones may have direct modulatory effects on neurotransmission. This has been particularly well characterised for the effects of corticosteroids on 5-HT neurotransmission (see McAllister-Williams and Young, 1998). The timescale of corticosteroid receptor responses, which is in hours, suggests steroids may not be directly involved in mechanisms of consciousness although longer term consequences of conscious processes may be registered as steroid interactions.

3.10 Nitric oxide

The most recently discovered neurotransmitter is the simplest molecule of all. Nitric oxide (NO) is synthesized from the amino acid arginine by the enzyme NO synthase (NOS). The NO signal transduction system has been most intensively studied in the cerebellum which has the highest level of NOS in the brain. Here, as a striatum, hypothalamus, cortex and hippocampus the enzyme occurs in populations of interneurons. However it also occurs in brainstem cholinergic neurons as part of the ascending reticular system projecting to the thalamus. NO is released in response to increases in intracellular calcium, following stimulation of receptors like glutamate (NMDA) which function as calcium channels. It thus has the potential to function as a kind of reverse transmitter, conveying information on the physiological status of the target neuron to its immediate input neurons. This may be relevant to emerging concepts that consciousness depends on recurrent/feedback (as opposed to feed forward) neuronal processing (Lamme and Roelfsema, 2000).

4.   Conclusion

The criteria proposed for a candidate transmitter correlate of consciousness, (Sec. 1) would appear, from information so far available, to be met most closely by activity of basal forebrain cholinergic systems. Modulatory effects of adenosine to inhibit these neurons is also likely to play a key role in controlling the level of consciousness. Mesolimbic dopaminergic activity throughout waking and dreaming may provide (via D2 and D3 receptors) an essential 'drive' mechanism without which there would be no conscious experience. It would be naïve to suggest that of the numerous transmitter systems outlined, only one or two govern conscious awareness — more likely cholinergic and dopaminergic projection pathways are necessary but not sufficient.

It could be argued that conscious awareness during waking and dreaming sleep are so radically different that the monoaminergic systems active mainly during waking contribute specifically to conscious awareness in this state. In addition, conscious awareness may, although experienced as a unitary process, be the product of component processes each governed by different systems. In any event, chemical transmission seems likely to be a key mechanism in integrating conscious awareness. According to Hoffer and Osmond (1964): "If any light is ever to be shed on the almost absolute darkness which envelopes these cerebral processes, then such light will only originate from chemistry and never from morphological research." The debate as to which of the different transmitters discussed in this chapter may be more central to consciousness is continued in subsequent chapters devoted to explorations of transmitter correlates of normal, drug-induced and pathological variations in consciousness.

Acknowledgements

References

Ameri, A. (1999). *Progress in Neurobiology* 58, 315–348.
Aston-Jones, G. et al. (1999). *Biological Psychiatry* 46, 1309–1320.
Baars, B.J. et al. (1998). *Trends in Neurosciences* 21, 58–62.
Berger, B. et al. (1991). *Trends in Neurosciences* 14, 21–27.

Blier, P. et al. (1998). *Annals of the New York Academy of Science* 861, 204–216.

Bogen, J. E. et al. (1995). *Cognition* 4, 52–62.

Breivogel, C.S. & S.R. Childers (1998). *Neurobiological Disorders* 5, 417–431.

Buzsaki, G. et al. (1988). *Journal of Neuroscience* 26, 735–744.

Byron, J. et al. (1993). *Psychic Experiences of the Famous.* Leicestershire: Tynron Press.

Calabresi, P. et al. (2000). *Trends in Neuroscience* 23, 120–126.

Callaway, E. & R.I. Band (1958). *Journal of Neurology and Psychiatry* 79, 91–102.

Coull, J.T. (1998). *Progress in Neurobiology* 55, 343–361.

Court, J.A. et al. (2001). *Journal of Chemical Neuroanatomy* 20, 281–298.

Delacour, J. (1995). *Neuropsychologica* 33, 1061–1074.

Di Marzo, V. et al. (1999). *Trends in Neuroscience* 21, 521–528.

Fernandex-Ruiz, J. et al. (2000). *Trends in Neuroscience* 23, 14–20.

Hampson, R.E. & S.A. Deadwyler (1999). *Life Sciences* 65(6–7), 715–723.

Herroelen, L. et al (1994). *Brain Research* 648, 222–228.

Hoffer, A. & H. Osmond (1964). *The hallucinogens.* New York: Academic Press.

Hokfelt, T. et al. (2001). *Journal of International Medicine* 249, 27–40.

Kinkead, B. et al. (1999). *Biological Psychiatry* 46, 340–351.

Lantos, T.A. et al. (1995). *Brain Research Brain Research Reviews* 20, 209–249.

Lamme, V.A. & P.R. Roelfsema (2000). *Trends in Neurosciences* 23, 571–579.

Lucki, I. (1998). *Biological Psychiatry* 44, 151–162.

McAllister-Williams, R.H. & A.H. Young (1998). In D. Ebert & K.P.E. Ebmeier (Eds.), *Advances in Biological Psychiatry*, vol. 19 [*New Models for Depression*] (170–198). Basel: Karger.

McCulloch, W.S. & W. Pitts (1943). *Bulletin of Mathematical Biophysics* 5, 115–133.

Mesulam, M.M. et al. (1995). *The Neurosciences* 7, 297–307.

Moreau, J.L. & G. Humber (1999). *Brain Research Reviews* 31, 65–82.

Oliver, B. et al. (2000). *Progress in Drug Research* 54, 61–115.

Parnavelas, J.G. (1990). *Progress in Brain Research* 85, 13–29.

Passani, M.B. et al. (2000). *Neuroscience and Biobehavioral Reviews* 24, 107–113.

Perry, E.K. & M.A. Piggott (2000). *Behavioural Brain Sciences.*

Perry, E.K. et al. (2000). *Trends in Neurosciences* 22, 273–280.

Porkka-Heiskanen, T. (1999). *Annals of Medicine* 31, 125–129.

Porritt, M.J. et al. (2000). *The Lancet* 356, 44.

Simmons, M.L. & C. Chavkin (1996). *International Review of Neurobiology* 39, 145–196.

Smith, D.F. (1999). *European Neuropsychopharmacology* 9, 537–544.

Ulett, G.A. et al. (1998). *Biological Psychiatry* 44, 129–138.

Verge, D. & A. Calas (2000). *Journal of Chemical Neuroanatomy* 18, 41–56.

Walker, J.M. et al. (1999). *Life Sciences*, 65, 665–673.

Wickelgren, I. (1997). *Science* 278, 35–37.

Wiley, J.L. (1999). *Pharmacology Biochemistry and Behaviour* 64(2), 257–260.

Woolf, N.J. (1997). *Consciousness & Cognition* (6), 574–596.

Young, A.H. et al. (1999). *Psychopharmacology* 145, 260–266.

Xiang, Z. et al. (1998). *Science* 281, 985–988.

Cholinergic transmission

Novel signal transduction

Nancy J. Woolf

1.   Introduction

The chemical anatomy of the brain offers clues regarding the nature of consciousness at the chemical level. In this regard, central cholinergic pathways are particularly well suited to unify the neural substrate of consciousness in the cerebral mantle. This is, in part, because cholinergic basal forebrain neurons form a compact aggregate that projects axons to all parts of the neocortex, hippocampus and amygdala (Fig. 2 in Chapter 1; Perry et al., 1999; Woolf, 1997). This kind of global anatomy is ideally suited to mediate non-local coherence and binding of activity across the cerebral mantle in stark contrast to the local, labeled-line anatomy typical of the glutamatergic sensory fiber tracts. Glutamatergic relays, especially those activating ionotropic glutamate receptors, elicit excitatory electrophysiological activity as their primary role. Arguably, only one excitatory neurochemical type is needed in the brain. Inhibitory neurons, such as those that use GABA, interact with both glutamatergic and cholinergic neurons and are discussed further in the latter context. What then is the primary purpose of other excitatory neurochemicals? Most central cholinergic receptors are metabotropic muscarinic types that activate many intercellular chemical cascades thereby suggesting that central cholinergic pathways may be best understood outside of a strictly electrophysiological framework.

Another reason to consider a novel role for the cholinergic basal forebrain is that cholinergic axons exhibit exquisite structural plasticity, similar to that of monoaminergic axons, and in marked contrast to that of glutamatergic axons (Farris et al., 1993; Woolf, 1996). Wholly new cholinergic axon branches bear-

ing multiple terminals can form *de novo* in adult brain. This is a different kind of plasticity than long-term potentiation (LTP), a form of increased synaptic efficacy often associated with the glutamatergic NMDA receptor. A high degree of structural plasticity that has the potential to endure beyond changes in synaptic efficacy such as occur with LTP, is arguably an essential feature of a system that mediates consciousness and memory function related to consciousness. A corollary of cholinergic terminal plasticity is found for cholinoceptive pyramidal cells of the cerebral cortex and hippocampus; these cells are enriched with cytoskeletal proteins—the dynamic integrators of structure and function (Woolf, 1993). Microtubule-associated protein-2 (MAP-2), in particular, exhibits memory-related plasticity that may indeed be related to consciousness (Woolf, 1997; 1998; Woolf et al., 1999). These cholinoceptive pyramidal cells also receive other neurochemical inputs that are likely to interact with the cholinergic input.

The main thesis of this paper is that the ultimate action of cholinergic cortical input is an effect on the intradendritic cytoskeletal matrix that mediates consciousness. An intradendritic site for consciousness contrasts with traditional electrophysiological models of consciousness. However, this thesis is compatible with the observation that patterns of electrophysiological activity may be largely unrelated to behavioral arousal (Vanderwolf, 2000). The most specific and plausible intradendritic events proposed to underlie consciousness involve quantum processes in dendritic cytoskeletal microtubules, outlined specifically in the model of "orchestrated objective reduction" (Orch OR) proposed by Penrose and Hameroff (Hameroff, 1998a; 1998b; Hameroff & Penrose 1996; 2000; Penrose, 1994; Penrose & Hameroff, 1995). The purpose of this paper is to show how the cholinergic system can interact with the cytoskeleton and support intradendritic quantum activities.

The available data are consistent with the present thesis that cholinergic inputs to cerebral cortex mediate intradendritic events fundamental to conscious activity as a primary role, and that cholinergic modulation of electrophysiological activity may be secondary, even epiphenomenal. Transduction pathways exist whereby muscarinic receptors (and possibly nicotinic receptors acting presynaptically to inhibit acetylcholine release) may lead to actions on the cytoskeleton directly relevant to consciousness. The thesis presented here describes these pathways and also suggests a possible explanation for the diversity of neuromodulators and metabotropic receptors. Accordingly, qualitative aspects of our consciousness would be finely tuned by a number of neurochemicals, prominent among which is acetylcholine.

2. The kind of anatomy needed to mediate conscious activity

Is there a certain kind of anatomy that is most likely to mediate conscious activity? Also, are there any kinds of anatomical arrangements that are unlikely to orchestrate the unified brain state we know of as consciousness? There are likely to be important constraints governing what is suitable anatomy for underlying consciousness in contrast to what kind of anatomy is favorably suited for unconscious information processing. These constraints are important clues as to how different neurochemical circuits divide up the manifold tasks taken on by the CNS.

The mammalian brain has certain patterns of connectivity that are found in virtually every species. This pattern includes a large number of labeled-line sensory pathways, beginning in each case at a receptor organ (i.e., retina, cochlea, vestibular organ, skin, muscle spindle, tendon organ, nasal mucosa and taste buds), and ending in almost every case in the cerebral cortex. Within the confines of that pathway's modality, labeled lines are specific (i.e., for a certain place in the visual field, for sounds of a particular pitch, a specific part of the body, a particular taste or a specific odor). By reducing sensory information into irreducible components, the function of sensory pathways is the antithesis of unification. We might also conclude that the operations of the sensory pathways are largely unconscious, and instead, it is the ideas we generate about sensory stimuli of which we are conscious. Consciousness or "knowing" is defined here along a continuum (Greenfield, 1995). It can potentially be vague, such as the knowledge that remains following brain damage known as "blindsight", or it can be as clear as full awareness of a well-illuminated visual scene. However, blindsight is often described as knowledge without consciousness, in contrast to vague awareness, the meaning assigned here.

The mammalian brain also possesses unifying anatomical circuits; this circuitry appears to derive from the basic motor circuit. Motor systems, for example, unify diverse motivations and sensations to drive singular purposeful actions. Anatomical circuits underlying sleep-wakefulness, attention, and memory also unify varied inputs into singular end states. Consciousness, which is a unified state, is likely to be similarly driven by anatomical circuits such as those that drive motor actions, arousal, selective attention and memory.

Neurochemicals distinguish the reductionistic-type sensory pathways from the integrative-type action circuitry. Sensory pathways commonly use the excitatory neurotransmitters glutamate or aspartate at virtually every relay. Most actions along these pathways are mediated by the fast acting glutamate receptors of the iontropic variety (i.e., AMPA and kainate receptors). Acetylcholine is

the most prevalent neurotransmitter found among the integrative-type action circuitry. Acetylcholine is the neurotransmitter at the neuromuscular junction, and centrally, acetylcholine and dopamine predominate in the basal ganglia. Acetylcholine, along with serotonin and norepinephrine, regulate sleep-wakefulness by acting through the circuitry of the ascending reticular activating system. The cholinergic basal forebrain, which may represent the rostral extension of the ascending reticular formation, is known to regulate cortical tone and to mediate selective attention and memory function. Coordinated regulation of cortical tone might be expected to lead to coherent activity. Hence the next section addresses the question of the extent to which the cholinergic basal forebrain mediates cortical binding and coherent activity?

2.1 Cholinergic basal forebrain mediation of binding and coherence in the cerebral cortex

The essence of consciousness is integrative, and as such, sensory information deriving from separate channels must be seamlessly melded into an instantaneous whole. Many neuroscientists agree that the synchronous gamma oscillation (e.g. ~40 Hz activity), resulting in temporal binding among cortical sites, is a correlate of conscious activity such as occurs with perception (Gray, 1999; Singer, 1999a; 1999b). It seems likely that gamma oscillations are necessary, but not sufficient, for consciousness. In this regard, acetylcholine is a prime candidate for inducing coherent gamma oscillations. Among the neuromodulators found in brain, only acetylcholine release is high during wakefulness and REM sleep and low during non-REM sleep, paralleling the presence of ~40 Hz activity (for review, see Kahn et al., 1997).

There are a number of studies showing that acetylcholine does indeed induce gamma oscillations, among other rhythms in the brain. For example, the cholinergic agonist carbachol, applied along with kainate, elicits gamma frequency oscillations in mouse somatosensory cortex in vitro (Buhl et al., 1998). Similarly, cholinergic activation induces gamma activity in rat hippocampal slices (Fellous & Sejnowski, 2000; Fisahn et al., 1998). Cholinergic deafferentation with the neurotoxin 192-IgG-saporin decreases, but does not completely abolish, electrocortical activity in the 20–44 Hz range; the spared cholinergic innervation to the amygdala may be responsible for the remaining coherent activity (Holschneider et al., 1999). It is presently not known how acetylcholine induces gamma oscillations. Cholinergic muscarinic activation might alter cortical cell firing patterns from tonic spiking to rapid bursting and this may be what underlies the induction of gamma activity (Wang, 1999).

It is clear, however, that it is the cholinergic input from the basal forebrain that is responsible for the activation of gamma activity. Injections of procaine or serotonin into the basal forebrain, both of which are inhibitory to cholinergic cells, result in decreased gamma activity; conversely, injections of excitatory glutamate agonist AMPA or norepinephrine into the cholinergic basal forebrain increase gamma activity (Cape & Jones, 1998; 2000). Injections of AMPA and norepinephrine into the cholinergic basal forebrain furthermore cause waking, the most rudimentary indicator of consciousness.

Muscarinic receptor activation of cortical pyramidal cells occurs with a latency of around 250 msec (Taylor & Brown, 1999). There is also an approximate 500 msec time lag between the occurrence of a stimulus and consciousness of that stimulus (Libet et al., 1991). Hence the typical delay associated with muscarinic action (and that of other metabotropic receptors) coincides with the time lag for stimuli reaching consciousness. Thus, cholinergic afferents to the cerebral cortex may contribute to 40 Hz activity, as well as to larger envelopes of activity (or inactivity) lasting 250–500 msec.

Acetylcholine released at select sites in the cerebral cortex would be expected to bring about a moment of unified consciousness much in the same manner that the coordinated activation of various muscle groups brings about a particular action. There is an assumed degree of flexibility as to which specific circuitry will be activated and in what order; however, it is the purposeful outcome that is of primary importance. To achieve this, acetylcholine must be able to markedly affect widespread cortical dynamics. Hence it is necessary that this neuromodulatory system: (1) have widespread projections to the entire cerebral cortex; including neocortex, hippocampus and amygdala; (2) provide distinct innervation to individual architectonic modules of cerebral cortex; and (3) specifically target cortical neurons involved in consciousness. How the cholinergic basal forebrain system fulfills these criteria is discussed in the next subsections.

2.2   Widespread projections of the cholinergic basal forebrain

The cholinergic basal forebrain constitutes a cellular aggregate, unlike a traditional brain region, insofar as cells do not form regularly shaped spheres resembling thalamic nuclei or an orderly layered structure such as cerebral cortex. Instead, cholinergic basal forebrain neurons appear to mingle, in an almost haphazard fashion, with fiber tracts passing through the general region (Fig. 1; Bigl & Arendt, 1991; Saper, 1990). Cholinergic neurons from different, yet overlapping, parts of the basal forebrain project to neocortex, hippocampus
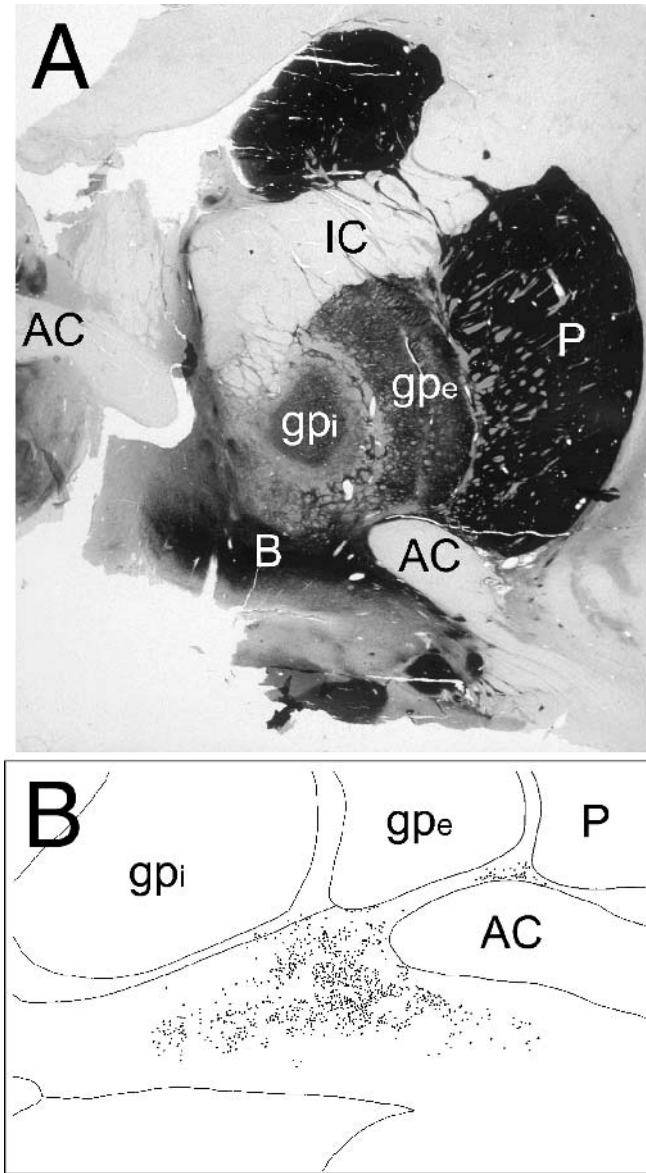
Figure 1. Frontal section through human brain stained for acetylcholinesterase (frame A) and diagram showing locations of individual cholinergic cells irregularly dispersed throughout the nucleus basalis of Meynert and surrounding regions of human brain (frame B). Abbreviations: AC, anterior commissure; B, nucleus basalis of Meynert; gp_e, globus pallidus external part; gp_i, globus pallidus internal part, IC internal capsule; P, putamen.

and amygdala (for reviews, see Butcher, 1995; Mesulam, 1995; Woolf, 1991). To the extent that cholinergic neurons make weak synaptic and possible dendrodendritic contacts with one another, the widely projecting cholinergic basal forebrain may behave as an integrated system controlling the pattern of activity throughout the cerebral mantle (see Woolf, 1991).

2.3 Nucleus basalis of Meynert: projections to the neocortex

In the human nucleus basalis of Meynert there are approximately one million basal forebrain cells. This relatively small number of cholinergic neurons, nonetheless, innervates a cortical sheet that would measure $\sim$0.5 m^2 if stretched fully out. Upon exiting the nucleus basalis of Meynert, cholinergic fibers reach the cerebral cortex through medial and lateral trajectories (Selden et al., 1998). The organizational plan of these projections in rat and non-human primate indicates each axonal arborization extends no more than 1–2 mm^2 in the horizontal plane and is furthermore confined within a single cytoarchitectonic field (Bigl et al., 1982; Price & Stern, 1983; Walker et al., 1985). This anatomical arrangement is unique to the cholinergic basal forebrain projection system, and as such it distinguishes the cholinergic system from the other diffuse afferent systems.

Although it is clear that the cholinergic basal forebrain exerts its influence mainly upon the cerebral cortex, it is less clear what influences the basal forebrain. Cholinergic cells in the nucleus basalis of Meynert receive synaptic inputs from cholinergic, catecholaminergic and GABAergic terminals (Smiley & Mesulam, 1999). Cholinergic inputs could come from other cholinergic basal forebrain cells or from cholinergic neurons in the mesopontine region (Carnes et al., 1990). Cholinergic and monoaminergic neurons in the mesopontine reticular core (i.e., the pedunculopontine and laterodorsal tegmental nuclei, the locus ceruleus and raphe nuclei; also known collectively as the ascending reticular formation) send axons to the cholinergic basal forebrain (Semba et al., 1988). As inferred from the known functions of the ascending reticular formation, these inputs probably regulate generalized arousal by modulating overall activity level in the cholinergic basal forebrain. These inputs to the basal forebrain cannot fully account, however, for the more specific responses of the cholinergic basal forebrain. For example, the inputs mentioned thus far cannot account for changes in basal forebrain activity triggered by visual stimuli as described in Wilson and Rolls (1990).

Cortical afferents to the cholinergic basal forebrain would provide the specific information required, but the extent to which the cortex innervates the

basal forebrain has remained controversial for some time. Recently, that controversy has been resolved, and it appears that although there may not be any direct contacts made by corticofugal cells upon cholinergic basal forebrain cells, the entire cerebral cortex may nonetheless input through GABAergic interneurons that, in turn, terminate upon cholinergic basal forebrain neurons (Zaborszky et al., 1997). Excitatory glutamatergic fibers originating in orbitofrontal and insular cortex terminate upon GABAergic cells lying next to cholinergic basal forebrain cells, but not upon the cholinergic neurons themselves. Neocortical axons terminate on striatal neurons that may, in turn, project onto cholinergic basal forebrain neurons; this is less clear. Afferents to the nucleus basalis arise from additional forebrain regions, such as the amygdala and hypothalamus; these afferents terminate directly upon cholinergic cell bodies (Zaborszky et al., 1984; Zaborszky & Cullinan, 1989). Many of these latter afferents appear to be glutamatergic or aspartatergic (Carnes et al., 1990).

2.4 Septohippocampal pathway and the cholinergic innervation of the amygdala

Cholinergic neurons in the medial septal nucleus and vertical diagonal band nucleus send axons mainly through the fornix that reach the hippocampus and the parahippocampal region (for review, see Woolf, 1991). Recently, the finer topography of these projections has been determined with multiple fluorescent dyes; the result being that the more rostral of these cholinergic neurons project to the dorsal hippocampus and the more caudal neurons project to the ventral hippocampus (Yoshida & Oka, 1995). The medial septal area receives similar kinds of inputs to those that the nucleus basalis receives. For example, the raphe nuclei project to both the hippocampus and the medial septal area (Acsády et al., 1996), and the supramammillary nucleus of the hypothalamus also provides glutamatergic or aspartatergic inputs to both the hippocampus and medial septal area (Kiss et al., 2000). The hippocampus sends axons to noncholinergic cells in the lateral and medial septal area; most of these recipient cells are GABAergic (Léránth & Frotscher, 1989).

Cholinergic cells in and around the horizontal diagonal band nucleus, which lies between the vertical diagonal band nucleus and the nucleus basalis, project to the amygdala (for review, see Woolf, 1991). As mentioned above, the amygdala sends axons to the basal forebrain, some of which terminate directly upon these cholinergic neurons (Zaborszky et al., 1984; Russchen et al., 1985). Cholinergic and catecholaminergic neurons in the mesopontine reticular core also project to this part of the basal forebrain (for review, see Woolf, 1991).

2.5 Cholinergic innervation of pyramidal cells

Cortical and hippocampal pyramidal cells are noteworthy in at least three ways: (1) they are preferentially, but not exclusively, innervated by cholinergic terminals; (2) they are implicated as a potential site of consciousness; and (3) they are enriched with cytoskeletal proteins, some of which undergo hyperphosphorylation in Alzheimer's disease. A novel signal transduction mode may exist within the large pyramidal cells of the cerebral cortex and hippocampus.

The large layer 5 pyramidal cells in the neocortex receive a significant portion of the cholinergic terminals arising from the basal forebrain. For one, these cells comprise the majority of the small population of cortical cells (∼15% of total cells) that are enriched with high levels of muscarinic receptor (van der Zee & Luiten, 1999; Woolf, 1993). The nature of this cholinergic contact has been resolved recently. Smiley et al., (1997) demonstrated that in human cortical slabs removed during surgery, 67% of cholinergic terminal varicosities appear to make synaptic contact, mainly with large layer 5 pyramidal cells. This does not, however, rule out a significant role for the non-synaptic release of acetylcholine as proposed by Descarries and colleagues (1997).

Multiple premises exist for the large layer 5 pyramidal cells being critical to consciousness. Crick and Koch (1992) have hypothesized that the large layer 5 pyramidal cells are correlated most closely with consciousness because they fire in bursts and send information completely out of the cortex. Hameroff and Penrose (1996) have suggested the cortical microtubule, tuned by the MAP-2 protein, as the site of conscious computation in the brain. This implicates the large layer 5 pyramidal cells because they are enriched with MAP-2 protein (Woolf, 1993).

Moreover, all cells are not equally targeted in Alzheimer's disease, a disease that has discernable effects on consciousness (Perry et al., 1999). Large pyramidal cells of the frontal and temporal cortex, as well as the large pyramidal cells in CA1 of hippocampus and subiculum, are the most susceptible to develop neurofibrillary tangles, to become dysfunctional and ultimately to die (Mann, 1996). It is the accumulation of abnormally hyperphosphorylated tau that disrupts the microtubular system of pyramidal cells in cortex and hippocampus both in experimental animal models and in Alzheimer's disease brain (Gong et al., 2000).

3. Muscarinic receptor activation of an intradendritic site mediating conscious activity

The hypothesis advanced in this chapter is that cholinergic innervation of the cortical pyramidal cell has as its main function an action upon consciousness, and that this is mediated through the long-term structural reorganization of MAP-2 and short-term regulation of the phosphorylation state of MAP-2 (Woolf, 1996; 1997; 1998). There is an advantage in proposing that synaptic activity occurs unconsciously and that a different mode of brain physiology accounts for consciousness. This proposal circumvents the problem of explaining emergence; namely, how consciousness (i.e., subjective awareness of self and environment) emerges from certain patterns of electrophysiological activity. The speculation that quantum entanglement might unite events occurring in neurons having no traditional axodendritic or axosomatic connections further removes the rather severe constraint of explaining how brain activity in different parts of the brain that are weakly connected or that have no connections whatsoever might be temporally bound together (Woolf, 1999b), for example, associating certain sights with certain sounds and smells.

The anatomy of central cholinergic pathways, as reviewed in the previous section, is vastly different from the labeled-line sensory pathways, the latter being ideally suited for information processing in perhaps an analogous manner to computations done on the present-day computer. The cholinergic basal forebrain is different, in that it does not receive direct input from any sensory pathway. As noted in the previous section, the cortex sends inputs to cholinergic basal forebrain neurons invariably through a GABAergic interneuron. This circuit, however, needs to be established for many parts of the neocortex. Cholinergic and monoaminergic cells of the ascending reticular core may provide indirect sensory information to the cholinergic basal forebrain, but here again many details need to be verified.

After many years of research it is still not established how the basal forebrain obtains the information it acts upon, but it seems to have access to "global knowledge" of both the internal and external environment related to the organism. It is presently hypothesized that this global knowledge may be attributable to (1) cell-to-cell contacts in the compact aggregate of cholinergic basal forebrain neurons that circulate information; (2) weak and indirect influences from the whole of the cerebral cortex; and (3) quantum entanglements in the cortex caused by microtubular coherence and collapse, that unify the cortical output to the basal forebrain.

By whatever means the cholinergic basal forebrain receives the information it does, this collective of neurons is in a position to affect future signal transduction relevant to consciousness in recipient pyramidal cells. The latter is likely to be through metabotropic muscarinic receptor activation of protein kinases that, in turn, affect MAP-2 binding to microtubules in recipient pyramidal cells (described in more detail in the next section). The main idea presented here is that there may well be a non-electrophysiological basis for the most basic, as well as the most complex, of cerebral functions: knowing. If the possession of knowledge, arguably the basis of higher consciousness, is indeed mediated non-synaptically through the metabotropic actions ultimately affecting the cytoskeleton, then the sheer complexity of this function might provide an explanation for why there are so many different metabotropic receptors.

4. Evidence for an intradendritic site mediated by cholinergic receptors

As discussed, acetylcholine (and perhaps some other neurotransmitters) may operate through metabotropic receptors to elicit a distinct mechanism that is synonymous with consciousness (i.e., Penrose-Hameroff Orch OR). This mechanism is proposed to occur through the regulation of the phosphorylation state of MAP-2 (see Fig. 2). Three supporting lines of evidence given here are: (1) non-neuronal acetylcholine facilitates organization of the cytoskeleton as a part of basic cell regulation; (2) MAP-2 is one of the most abundant group of proteins in mammalian brain; and (3) a number of protein kinases that are activated by metabotropic receptors, in turn, affect the phosphorylation state of MAP-2, thereby altering its binding to microtubules.

Acetylcholine is in evolutionary terms an extremely old molecule, being found in such primitive organisms as blue-green algae, yeast and fungi as to suggest its presence some 3 billion years ago (for review, see Wessler et al., 1999). Many non-neuronal cells contain acetylcholine. Along with directly organizing the cytoskeleton, many non-neuronal functions of acetylcholine indirectly involve the cytoskeleton (e.g., mitosis, differentiation, locomotion, migration, cell-to-cell contact). It is likely that neuronal functions of acetylcholine were built upon this foundation of earlier roles.

The neuronal cytoskeleton plays a number of roles, such as providing structural support and transporting organelles; however, the idea that it is a transduction site is relatively recent (Quinlan & Halpain, 1996; Sánchez et al., 1999; Woolf, 1999a). The MAP-2 molecule may play a primary role in this regard because it binds not only to the microtubular matrix, but also to micro-
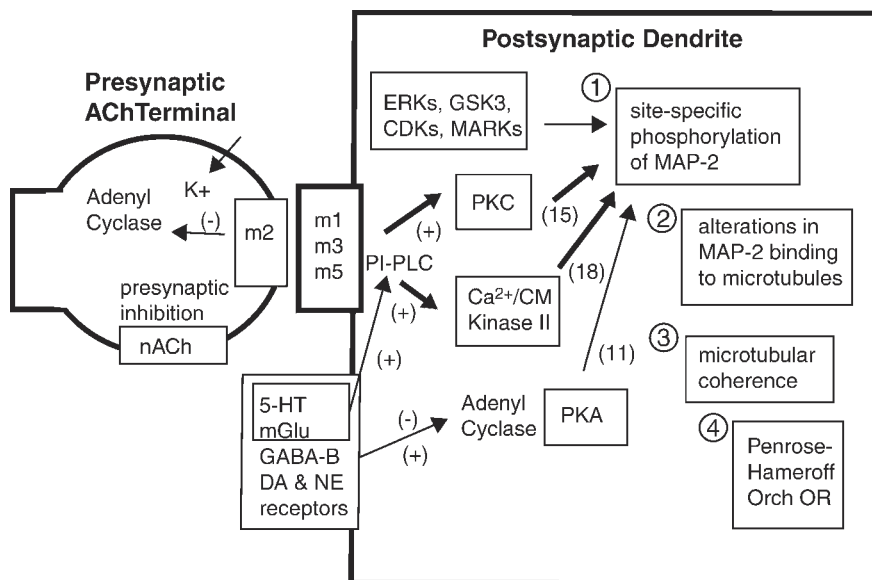
Figure 2. Schematic diagram of the metabolic pathways activated by cholinergic input to a dendrite of a cortical pyramidal cell. Postsynaptic inputs mediated by muscarinic receptors (m1, m3, and m5) increase phosphoinositide-specific phospholipase C (PI-PLC), which in turn activates protein kinase C (PKC) and calcium/calmodulin-dependent kinase II (Ca^{2+}/CM kinase II), which in turn induces site-specific phosphorylation at 15 and 18 sites respectively (heavy arrows). These signal transduction pathways lead to (1) site-specific phosphorylation of MAP-2, (2) alterations in MAP-2 binding, (3) microtubular coherence (or decoherence), and under sufficient conditions (4) Penrose-Hameroff Orch OR (Hameroff and Penrose, 1996; 2000; Penrose and Hameroff, 1995). Light arrows designate presynaptic actions of muscarinic (m2) and nicotinic (nACh) acetylcholine receptors, postsynaptic actions of metabotropic receptors binding other transmitters (serotonin, 5-HT; glutamate, mGlu; GABA, GABA-B; dopamine, DA; norepinephrine, NE) that largely affect protein kinase A (PKA), and additional families of kinases (ERKs: extracellular signal-related kinases; GSK3: glycogen-synthase kinase 3; CDKs: cyclin-dependent kinases; MARKs: MT-affinity regulating kinases). Some or all of these pathways may interact with the cholinergic activation of signal transduction pathways leading to MAP-2 mediated effects. For more details on kinase actions upon MAP-2 see Sánchez et al. (1999).

filaments and neurofilaments. MAP-2 also regulates plasticity underlying axonal and dendritic growth during development, as well as dendritic and synaptic reorganization in the adult (Johnson & Jope, 1992; Sánchez et al., 1999; Woolf, 1998). There may be a link between these two roles for MAP-2. Struc-

tural changes in MAP-2 bridges with microtubules can modify the bundling of microtubules and microtubular length (Sánchez et al., 1999). Structural reorganization of these types may encode for the content of memory, retrieved as a conscious event in the restructured microtubules (Woolf, 1997; 1998).

Conscious retrieval of memory would thus involve a search through the entire neocortex, hippocampus and amygdala executed through the modulation of acetylcholine release. Acetylcholine is known to activate postsynaptic muscarinic receptors (m1, m3, m5) located on the pyramidal cell membrane (Levey, 1996; Taylor & Brown, 1999). As shown in Fig. 2, postsynaptic muscarinic receptors activate phosphoinositide-specific phospholipase C (PI-PLC) that, in turn, activates protein kinase C (PKC) through a GTP-binding protein and releases calcium from internal stores, thereby activating Ca^{2+}/calmodulin-dependent kinase II. There are also presynaptic receptor (m2) actions influencing axon terminal release of acetylcholine, including inhibition of adenylate cyclase resulting in a decrease in protein kinase A (PKA) and a rapid influx of K^+. The m4 receptor may not play a role in this particular circuit (Levey, 1996).

Muscarinic receptor actions have potential effects on the phosphorylation state of MAP-2 protein (for review of MAP-2 phosphorylation, see Sánchez et al., 1999). MAP-2 is shown to be a substrate for Ca^{2+}/calmodulin-dependent kinase II and for PKC, the former mediating phosphorylation at as many as 18 binding sites on the MAP-2 protein, and the latter mediating phosphorylation at as many as 15 sites (Walaas & Nairn, 1989). The way in which phosphorylation can inhibit tubulin polymerization and microtubule formation is not fully understood; however, it appears that PKC is responsible for phosphorylation at binding sites Ser-1703, Ser-1711 and Ser-1728, which dramatically inhibits MAP-2 binding with microtubules (Ainsztein & Purich, 1994). Alterations in the phosphorylation state of MAP-2 would be expected to affect its binding to microtubules, thereby affecting microtubular coherence and Penrose-Hameroff Orch OR (Fig. 2, steps 1–4).

As shown in Figure 2, monoamine transmitters and, in some cases, glutamate bind to metabotropic receptors that activate or inhibit adenylate cyclase, and this affects MAP-2 phosphorylation through PKA. In addition to these effects, certain 5-HT and metabotropic glutamate receptors exert effects similar to those triggered by m1, m3 and m5 muscarinic receptors; namely they activate PI-PLC (Dingledine & McBain, 1999; Frazer & Hensler, 1999). The importance of PI-PLC, especially in combination with PKC, as a mechanism underlying consciousness is underscored by results of volatile anesthetics inhibiting its coupling to metabotropic receptors (Durieux, 1995; Minami et al., 1997).

5.   Revising the concept of neuromodulation

The concept of neuromodulation has been previously focused on the distinction between fast versus slow, direct versus indirect, and straightforward versus complex actions in the brain. Metabotropic actions mediated though central cholinergic and monoaminergic neurotransmitters have frequently been termed neuromodulatory due to their slow, indirect and complex natures. Cooper et al. (1996) define neuromodulation as the case where the "ultimate effect is a change in the firing pattern of the postsynaptic neuron." In this paper, the hypothesis is advanced that neuromodulators, such as acetylcholine, and their actions on metabotropic receptors will best be understood by viewing their direct effects on consciousness as mediated through the regulation of the phosphorylation state of MAP-2, which affects MAP-2 binding to the microtubule and then affects microtubule coherence and collapse according to the Penrose-Hameroff Orch OR model. The anatomy of the cholinergic afferents provides widespread, modularly organized inputs to the cerebral mantle consistent with a role of simultaneously triggering a conscious mechanism in multiple dendrites of diverse cortical modules.

A better understanding of the neurochemistry of consciousness is likely to lead to a more accurate assessment of the fundamental basis of therapeutic drug action in psychiatric illness, as well as to increase our understanding of Alzheimer's disease and normal cognition. A novel approach may be needed to make further progress in this regard.

Acknowledgements

References

Acsády, L.D. et al. (1996). *Biologica Hungarica* 47, 9–19.
Ainsztein, A.M. & D.L. Purich (1994). *Journal of Biological Chemistry* 269, 28465–28471.
Bigl, V. & T. Arendt (1991). *Acta Psychiatrica Scandinavica. Supplementum* 366, 7–13.
Bigl, V. et al. (1982). *Brain Research Bulletin* 8, 727–749.
Buhl, E.H. et al. (1998). *Journal of Physiology* 513, 117–126.
Butcher, L.L. (1995). *The Rat Nervous System, Second edition.* (1003–1015). London: Academic Press.

Cape, E.G. & B.E. Jones (1998). *Journal of Neuroscience* 18, 2653–2666.

Cape, E.G. & B.E. Jones (2000). *European Journal of Neuroscience* 12, 2166–2184.

Carnes, K.M. et al. (1990). *Journal of Comparative Neurology* 302, 824–852.

Cooper, J.R. et al. (1996). *The Biochemical Basis of Neuropharmacology, 7th Ed.* New York: Oxford University Press.

Crick, F. & C. Koch (1992). *Scientific American* 267, 152–159.

Descarries, L. et al. (1997). *Progress in Neurobiology* 53, 603–625.

Dingledine, R. & C.J. McBain (1999). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Sixth Edition* (213–242). Philadelphia: Lippincott-Raven.

Durieux, M.E. (1995) *Anesthesiology* 82, 174–182.

Fellous, J.M. & T.J. Sejnowski (2000) *Hippocampus* 10, 187–197.

Farris, T. W. et al. (1993). *Hippocampus* 10, 187–197.

Fisahn, A. et al. (1998). *Nature* 394, 186–189.

Frazer, A. & J.G. Hensler (1999). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Sixth Edition* (263–292). Philadelphia: Lippincott-Raven.

Gong, C.X. et al. (2000). *Journal of Biological Chemistry* 275, 5535–5544.

Gray, C.M. (1999). *Neuron* 24, 31–47.

Greenfield, S.A. (1995) *Toward a science of consciousness*. New York: W. H. Freeman & Company.

Hameroff, S. (1998a) *Trends in Cognitive Sciences* 2, 119–127.

Hameroff, S. (1998b) *Philosophical Transactions Royal Society London (A)* 356, 1869–1896.

Hameroff, S. & R. Penrose (1996). *Toward a Science of Consciousness – The First Tucson Discussions and Debates* (507–540). Cambridge, MA: MIT Press.

Hameroff, S. & R. Penrose (2000). *Annals of the New York Academy of Sciences,* in press.

Holschneider, D.P. et al. (1999). *Experimental Brain Research* 126, 270–280.

Johnson, G.V.W. & R.S. Jope (1992). *Journal of Neuroscience Research* 33, 505–512.

Kahn, D. et al. (1997). *Neuroscience* 78, 13–38.

Kiss, J. et al. (2000). *Neuroscience* 97, 657–669.

Léránth, C. & M. Frotscher (1989). *Journal of Comparative Neurology* 289, 304–314.

Levey, A.I. (1996). *Proceedings of the National Academy of Sciences of the United States of America* 93, 13541–13546.

Libet, B. et al. (1991). *Brain* 114, 1731–1757.

Mann, D.M. (1996). *Neurodegeneration* 5, 423–427.

Mesulam, M.-M. (1995). *Psychopharmacology: The Fourth Generation of Progress* (135–146). New York: Raven.

Minami, K. et al. (1997). *Journal of Pharmacology and Experimental Therapeutics* 281, 1136–1143.

Penrose, R. (1994). *Shadows of the Mind: A Search for the Missing Science of Consciousness.* Oxford & New York: Oxford University Press.

Penrose, R. & S. Hameroff (1995). *Journal of Consciousness Studies* 2, 99–112.

Perry, E.K. et al. (1999). *Trends in Neurosciences* 22, 273–280.

Price, J. L. & R. Stern (1983). *Brain Research* 269, 352–356.

Quinlan, E. M. & S. Halpain (1996). *Neuron* 16, 357–368.

Russchen, F.T. et al. (1985). *Journal of Comparative Neurology* 242, 1–27.

Sánchez, C.J. et al. (2000). *Progress in Neurobiology* 61, 133–168.

Saper, C.B. (1990). *The Human Nervous System* (1095–1114). San Diego: Academic.

Selden, N.R. et al. (1998). *Brain* 121, 2249–2257.

Semba, K. et al. (1988). *Journal of Comparative Neurology* 267, 433–453.

Singer, W. (1999a). *Neuron* 24, 49–65.

Singer, W. (1999b). *Nature* 397, 391–393.

Smiley, J. F. & M.-M. Mesulam (1999). *Neuroscience* 88, 241–255.

Smiley, J.F. et al. (1997). *Experimental Neurology* 144, 361–368.

Taylor, P. & J.H. Brown (1999). *Basic Neurochemistry: Molecular, Cellular and Medical Aspects, Sixth Edition* (213–242). Philadelphia: Lippincott-Raven.

van der Zee, E.A. & P.G. Luiten (1999). *Progress in Neurobiology* 58, 409–471.

Vanderwolf, C.H. (2000). *Brain Research* 855, 217–224.

Walaas, S. I. & A.C. Nairn (1989). *Journal of Molecular Neuroscience* 1, 117–127.

Walker, L.C. et al. (1985). *Brain Research Bulletin* 15, 307–314.

Wang, X. J. (1999). *Neuroscience* 89, 347–362.

Wessler, I. et al. (1999). *Clinical and Experimental Pharmacology and Physiology* 26, 198–205.

Wilson, F. A. W. & E.T. Rolls (1990). *Experimental Brain Research* 80, 104–120.

Woolf, N.J. (1991). *Progress in Neurobiology* 37, 475–524.

Woolf, N.J. (1993). *Journal of Chemical Neuroanatomy* 6, 375–390.

Woolf, N.J. (1996). *Neuroscience* 74, 625–651.

Woolf, N.J. (1997). *Consciousness and Cognition* 6, 574–596.

Woolf, N.J. (1998). *Progress in Neurobiology* 55, 59–77.

Woolf, N.J. (1999a). *Trends in Neurosciences* 22, 540–541.

Woolf, N.J. (1999b). *Consciousness and Cognition* 8, 574–596.

Woolf, N.J. et al. (1999). *Brain Research* 821, 241–249.

Yoshida, K. & H. Oka (1995). *Neuroscience Research* 21, 199–209.

Zaborszky, L. & W.E. Cullinan (1989). *Brain Research* 479, 177–184.

Zaborszky, L. et al. (1997). *Neuroscience* 79, 1051–1078.

Zaborszky, L. et al. (1984). *Neuroscience Letters* 52, 219–225.

Natural Alterations of Consciousness

CHAPTER 3

Attention

Andrew Scholey

1. Introduction

Attention and the related phenomenon of arousal are clearly crucial to the generation of consciousness. Both processes contribute to the (everyday) experience of the focus and level of awareness. Many reviews of attention begin with the following quotation from William James: "Everyone knows what attention is. It is the taking possession of the mind, in clear and vivid form, of one out of what seem several simultaneously possible objects or trains of thought." (James, 1890). The enduring resonance of this definition is due to its encapsulation of the essence of the subjective experience of attention. James emphasises the fact that attention selects stimuli from a surplus of environmental information ("simultaneously possible objects"), and may be focussed perceptually or inwardly as a "train of thought." Of particular relevance to the present chapter, the quotation continues. . . . "Focalization, *concentration of consciousness* are of its essence" [italics added]. Indeed, superficially one might even suggest that the terms consciousness and attention may be used synonymously. However this apparent equivalence does not hold up to even cursory scrutiny—while arousal and attention may necessary for certain aspects of consciousness they are far from sufficient. In addition, there is also implicit attention underpinning nonconscious cognition. Nevertheless we can start with the presumption that consciousness is to some degree quantified by arousal while qualified by attention.

2. Theories of attention

As psychological and neurochemical empiricism became refined during the twentieth century, it became clear that attention is not a unitary process. Writ-

ing a century after James, Alan Allport (1993) stated that "There can be no simple *theory of attention*, any more than there can be a simple *theory of thought*. A humbler but more ambitious task for the next 25 years will be to characterize, in cognitive neurobiological terms, as much as possible of this great diversity of attentional functions." It is beyond the scope of this chapter to provide a complete explanation of the neuroanatomical and neurochemical substrates of these various "attentional functions." Rather it will attempt to provide a flavour of psychological models and measures of attention, to relate these to activity in neuroanatomical substrates and to describe known attentional dissociations following psychopharmacological interventions. For more detailed descriptions of the neural correlates and psychopharmacology of attention the reader is directed towards a number of excellent reviews, including Coull (1998), Robbins (1997) and Tiplady (1996).

2.1 Psychological models

Limited sense organ receptivity dictates the range of biologically relevant stimuli which can be processed to any level by an organism (thus the human retina is sensitive to a portion of the electromagnetic radiation lying in the range 380 nm to 760 nm). Early models of attention identified a number of stages between sensory detection and the performance of cognitive operations (conscious or unconscious) upon resultant representations of these stimuli. The passage from one operational stage to another may depend on both decay of neural representations and on stage-specific filtering. The extent to which stimuli are further processed is dictated by a series of neural, cognitive and information-processing mechanisms and early theories of attention attempted to account for the degree to which stimuli survive to the next stage. A further question relates to the extent to which such processing is under conscious voluntary control or even available to conscious awareness.

2.2 Early and late selection models

Earlier theories of attention such as that proposed by Broadbent (1958) suggested that some physical property of sensory stimuli dictates whether or not they are available to further processing (Fig. 1). Crucially Broadbent considered attention to be a real *physical* property of the nervous system, not a convenient psychological construct or metaphor. In this formulation early selection of stimuli is performed by a limited capacity filter and only selected stimuli are encoded. While this and similar models paved the way for experimental re-
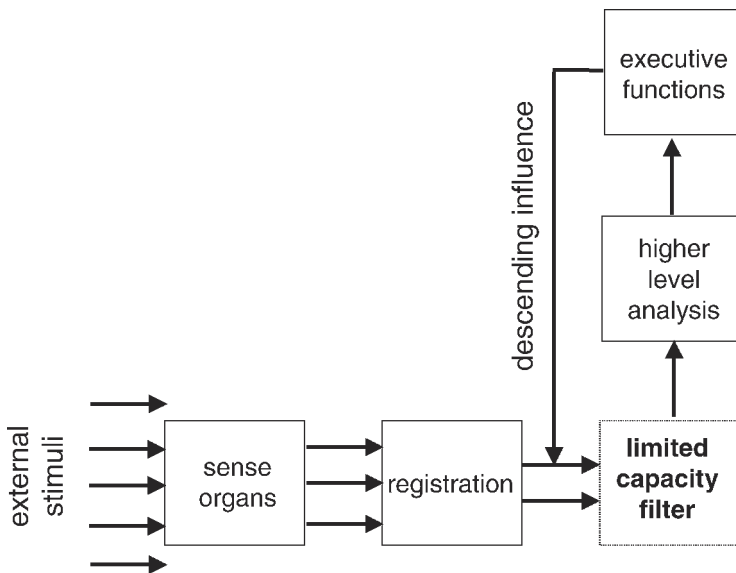
Figure 1. An example of an early selection model of attention based on Broadbent (1958). Following registration of stimuli, a limited capacity filter determines which stimuli are available for further, higher level analysis. The properties which determine the nature of filtering may be modified by descending influences.

alisation of attentional models, such strict *early-selection* models of attention could not account for certain everyday phenomenon, famously including the 'Cocktail Party' effect. Here one is able to direct attention (or stream of consciousness) towards one conversation amongst many, but will become aware of other salient stimuli (e.g. one's name) in unattended "channels." Related laboratory studies included those using a dichotic listening paradigm developed by Cherry (1953). Here subjects are made to attend to a stimulus stream presented to one ear by "shadowing"—that is immediately repeating—the input. Such attention is readily performed and a different conversational train presented to the non-attended ear is easily ignored. However subjects will become aware of a salient stimulus (for example a familiar name or an overtly sexual word) presented to the non-attended ear. Moreover if the meaning of a sentence is switched from one ear to another, attention will also, effortlessly, switch. Such results emphasise the similarities between consciousness and attention in terms of their "binding" properties.

Observations which could not be accommodated within a simple, limited capacity filter model led to the development of *late-selection* theories of atten-
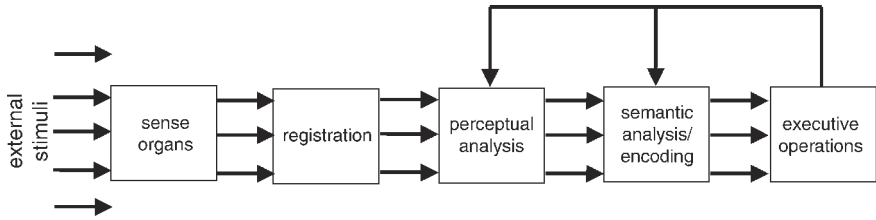
Figure 2. Late selection models of attention suggested that even information in unattended 'channels' may be processed to the level of semantic encoding. Again descending influences play a modulatory part at later stages.

tion by workers including Treisman (1969) and Broadbent (1971). Such theories suggest that streams of information which are not consciously attended are nevertheless processed, albeit in a much attenuated fashion (Fig. 2). The degree of attenuation is negatively related both to the salience of unattended stimuli and the level of available cognitive resources. Thus attention appears to be limited by the availability of processing resources and by effort (Kahneman 1973). Here the notion arises that sustaining attention is associated with some sort of cost; hence, at some level, during conscious focus one really is 'paying' attention. The extent to which this attentional economy maps onto neural substrates may uncover important relationships between conscious states and physical processes.

2.3 Supervisory systems

Control of the attentional processes described above has been variously assigned to a Central Executive (Baddeley, 1995) or to a Supervisory Attentional System within Shallice's formulation (Norman & Shallice, 1986). Shallice's model proposes that control of attention is processed with respect to dynamic situation-specific processes of anticipation (planning of strategy), and flexibility and inhibition (both of which impose and regulate strategy). With respect to both Shallice's Supervisory Attentional System and Baddeley's Central Executive model, and paralleling an earlier statement, van Zomeren and Brouwer (1994) suggest that attentional processes are *qualified* by selection and *quantified* by intensity. Thus roles of attentional systems may be specified with respect to conscious states. Effective working of the supervisory attentional system depends on the integrity of the anterior cingulate. Activation of this region has been recorded during functions allocated to the system by Norman and Shallice (Posner, 1994). Interestingly these processes are somewhat

akin to what James termed "willed" acts or those involving "an additional conscious element, in the shape of a fiat, mandate or express consent" as distinct from "ideo-motor" acts where the actor is "aware of nothing between the conception and the execution" (James, 1890). In Shallice's model such deliberate attentional resources are needed in five situations including: to novel situations requiring planning or decision making; during situations requiring error correction; when the situation is not familiar or well learned; in dangerous or difficult situations; and when the situation calls for a response which competes with a learned response.

2.4 Specific measures

While the above models of attention have proved fruitful for realisation of attentional systems, other experimental approaches (particularly psychopharmacology) has tended to group attentional processes into interacting systems which have been classified in various ways. Perry and Hodges (1999) identify three subsystems of *selective attention*, *sustained attention* and *divided attention*. Selective attention requires a capacity to focus and 'close' on one stimulus stream or feature, while attenuating the distracting effect of competing information and has strong parallels with the theatre metaphor of consciousness. In the laboratory, dichotic listening is an example of selective attention, as is the Stroop paradigm (Stroop, 1935). Here subjects read words describing colours printed in different (congruous or incongruous) coloured ink. They are required to attend to one stimulus feature (colour) while other, competing, features (word) are ignored, the relative difficulty in reading incongruous colour-words compared to congruous ones is the Stroop effect (Stroop performance requires deliberate attentional resources within Shallice's model described in the previous section). Sustained attention requires 'holding' attention over relatively long periods of time and has features of vigilance. Sustained attention underlies competent performance of tasks requiring signal detection over long periods such as the Rapid Visual Information Processing task where a subject is presented with single digits at a high rate (typically 100/minute) and is required to respond to three consecutive even or three consecutive odd digits. Divided attention refers to the ability to perform two or more tasks simultaneously and may be considered as requiring the opposite operations to selective attention. For example a subject may be presented with stimuli which vary with respect to colour, motion and shape and monitor changes in all three dimensions (Corbetta et al., 1991).

Other investigations have tended to concentrate on cognitive processes involved in specific aspects of attention. One example which has been widely used to study the neural substrates of attention involves directing visual attention. Covert orientation describes the phenomenon of directing attention without obvious (overt) attention to stimuli. In an early introspective precursor to later experiments, in 1894 Herman von Helmholtz observed that attending to a small field amongst a large array of stimuli (while fixating elsewhere) led, during brief flashes of light, to the perception of the attended stimuli only. Helmholtz concluded that "… one can concentrate attention on the sensation from a particular part of our peripheral nervous system and at the same time exclude attention from all other parts." One fruitful paradigm which has been used extensively to investigate the control of this covert 'spotlight' of visual attention was developed by Michael Posner (e.g. Posner & Peterson
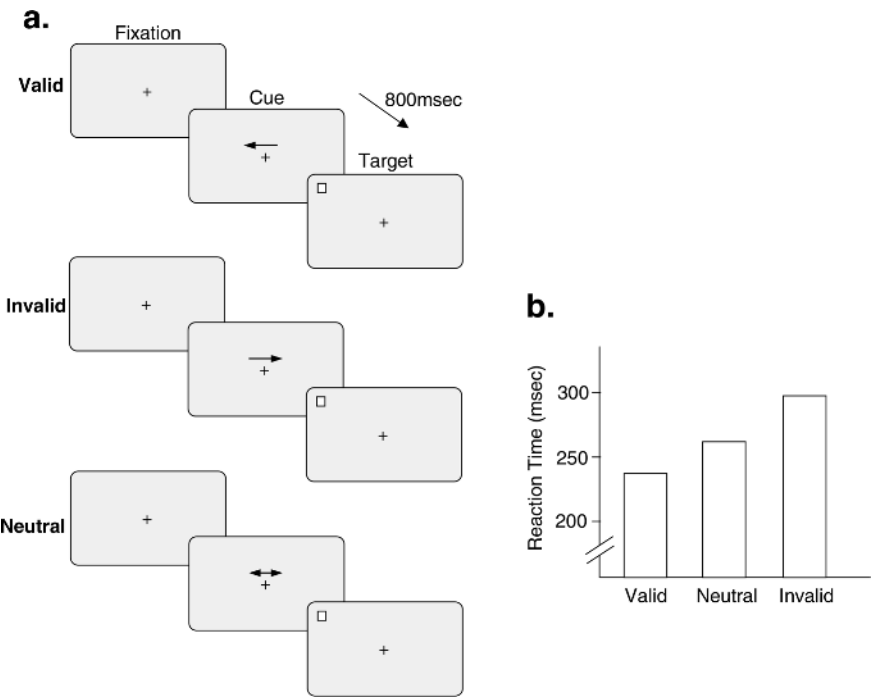

Figure 3. The covert orientation of attention paradigm. a) Subjects visually fixate on the central cross throughout. A cue (in this case a central arrow), which may be valid, invalid or neutral directs attention to the correct, incorrect or neither target location respectively. b) The typical cost and benefit of valid and invalid cueing.

1990). In the covert orientation of attention task (Fig. 3) subjects fixate on a central point on a computer screen (3a) and stimuli are presented to the left or right of this point following a signal (a central arrow pointing left or right) which diverts attention, but not gaze (hence 'covert'), to the signalled or unsignalled side. There is a brief interval (typically 800 msec) between signal and stimulus, and response time to react to the stimulus is taken as an index of attentional performance. The typical cost and benefit of such valid and invalid cueing, measured as slowed and speeded response times relative to a non-directional cue respectively, is presented in Figure 3(b). The beauty of this paradigm is that it clearly involves the conscious, voluntary selective direction of attention, and allows differentiation of attentional and perceptual orientation.

Posner and colleagues have delineated a number of brain regions which underlie processes involved in controlling attentional focus and switch which are discussed in later sections. These include disengagement of attention (involving the right superior parietal lobe), followed by a shift in the field of attention (superior colliculus), and an enhancement of the target (pulvinar region of the thalamus). The neural substrates are examined in later sections, while the cog-
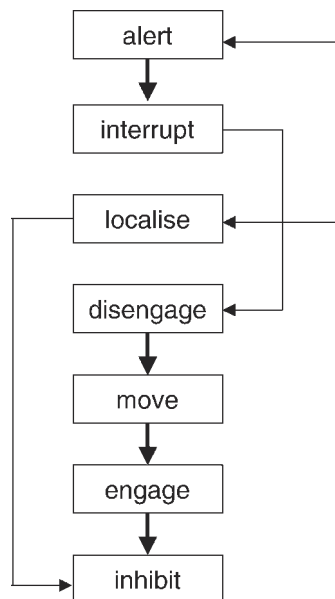

Figure 4. The three-stage model of Posner et al. (1984) showing the processes involved in shifting attention from one spatial location to another.

nitive structures and processes involved in this three-stage model are presented schematically in Figure 4.

3. Electrophysiology

3.1 EEG

Investigations into the neural substrates of attention have been facilitated greatly by brain imaging techniques. In such studies good temporal resolution is paramount and so the electroencephalogram (EEG) has proved invaluable. Briefly, EEG activity within high frequency alpha and beta (8–30 Hz) and low frequency delta and theta (less than 8 Hz) bands is believed to be a manifestation of cortical arousal. Specifically, activity in the high frequency spectra is reduced with the onset of sleep, while that of the low frequency bands increase. Similar changes are observed following the repeated performance of a task suggesting that sustaining attention (vigilance) may engender lower arousal levels (Parasuraman, 1984).

3.2 ERP

Event-related potentials (ERPs) describe coherent, replicable changes in cortical electrical activity which are time-locked to stimuli (events). The N1 potential is a sensory-evoked, early negative waveform usually with a latency of less than 90 msec. In an auditory attention paradigm, the amplitude of the N1 was increased to stimuli presented to the attended ear as opposed to the unattended ear (Hillyard et al., 1973). Such results provide evidence for some degree of early selection (based here only on which ear is attended). Later studies using co-registered ERP, magnetoencephalography (MEG) and magnetic resonance imaging (MRI) suggest that this earliest modulation of auditory inputs occur within Heschl's gyri of the auditory cortex (Woldorff & Hillyard, 1993). Regarding visual selective attention, using the covert orientation paradigm (Fig. 3), orientation towards a stimulus was associated with modulation of both the N1 and the early positive P1 waveforms, again as early as 70–90 msec following stimulus onset (Hillyard et al., 1995). In particular, the N1 component was similar following invalid and neutral cues, but was potentiated for valid cues; while the P1 component was similar for valid and neutral cues, but attenuated for invalid cues (Luck et al., 1994). These effects have been interpreted as reflecting the optimisation of the signal-to-noise ratio, within extrastriate

association areas, prior to further (visual) attentional processing. During early attentional processing the N1 component is associated with an amplification of the signal while the P1 component reflects a reduction in noise.

Further, higher order attentional processing of stimuli (including for example attending to colour, spatial frequency, orientation or semantics) is associated with the modulation of later waveforms (>200 msecs). The most widely researched evoked potential is the P300. In a paradigm where subjects attend to an auditory stream (a series of tones) played in one ear while ignoring different tones inputted simultaneously to the other, the P300 is potentiated by 'oddball' stimuli—an occasional different tone in the attended stream. The P300 waveform is modulated by attention, having a larger amplitude when an attentional task is more demanding. Conversely, P300 latency is taken to be an index of stimulus evaluation and categorisation and may reflect the updating of working memory (Donchin & Coles, 1988; Coles et al., 1995). Interestingly, in James' description consciousness may be something akin to modern conceptualisations of working memory, that is whatever one is aware of at any given moment may be some manifestation of the contents of working memory (but see Dennett (2001) for a robust argument against this contention).

4. Neuroanatomy

The activity modulations described above map onto a putative attentional network which is modulated by arousal as controlled by the ascending reticular formation. The mammalian attentional network is subserved primarily by subcortical (thalamic), and by frontal and parietal structures. Thus the superior parietal cortex is activated when attention is switched from one location to another—either through voluntary control (covert switching), or when there is a degree of automaticity including during searching through a field of potential targets (Corbetta et al., 1993; 1995). Neurons from such cortical 'control' areas send axonal projections to cells in sensory-specific cortical areas and alter their excitability. Thus a circuit comprising of pulvinar, posterior parietal cortex, and the dorsolateral prefrontal cortex mediates cortical excitability in the extrastriate cortex as a function of selective (visual) attention (see below).

The inferior longitudinal fasciculus follows the 'ventral stream' and involves a pathway conjoining the primary visual cortex with the inferior temporal cortex. It is believed to be involved in object identification by integrating feature analysis with object discrimination. Single cell recordings from area V4 of the extrastriate cortex during covert orientation of attention reveal an in-

creased firing rate during attention to (but not mere perception of) stimuli within the neuron's visual field (Moran & Desimone, 1985). In later stages of feature analysis by ventral stream neurons a different firing pattern occurs. In primates there is a massive amount of neuronal projection from the visual cortex back to the thalamus. These projections synapse onto neurons within the reticular nucleus of the thalamus (specifically for the visual system these influence cells of the perigeniculate nucleus which surrounds the lateral geniculate nucleus). The reticular nucleus maintains complex interactions with neurons in thalamic relays and is thus well placed to gate the flow of information from thalamus to cortex (Yingling & Skinner, 1976), and control of this gate by the ascending reticular pathway undoubtedly plays a crucial role in arousal. Crick has also implicated such processes in selecting the location of visual field for the spotlight of attention during perception (Crick, 1992). However their role in voluntary attention is not known.

Amongst other subcortical structures, neurons of the superior colliculus are involved in saccadic eye movements and attentional processes (Wurtz et al., 1982). Local deactivation of the superior colliculus decreases attentional task performance only in the presence of distractors. Again there appears to be a critical interaction between attention and arousal, with a specific attentional role for this particular locus remaining unclear.

The pulvinar nucleus of the thalamus, which has no known role in the retinal-primary visual cortex pathway, has more attentional specificity. It is ideally placed structurally and functionally to maintain reciprocal connections with cortical and subcortical areas. With respect to visual attention this structure may therefore facilitate the influence of extrastriate visual cortex processing by frontal and parietal cortices. The primate pulvinar is activated only during attentional filtering, and not during perception alone. The structure contains cells which are differentially sensitive to colour, motion and orientation, and its subdivisions have retinotopic representations of the visual world. Furthermore the pulvinar has projections to all four cortical lobes. The work of Peterson, Robinson and colleagues suggests that the pulvinar is involved in the attenuation of irrelevant information. For example in humans the pulvinar is activated during tasks where maintaining performance relies on effective filtering of distractors (LaBerge, 1990).

The parietal cortex plays a specific role in spatial attention and has received a great amount of scrutiny. The posterior parietal cortex is the target for many neurons following the superior longitudinal fasciculus or 'dorsal stream'. The firing rate of parietal neurons increases during fixation on visual stimuli, during saccades or during directing covert attention (Mountcastle, 1976). The

structure is active during covert reorientation and appears to be involved in the control of voluntary shifts in attention. Parietal lobe damage is commonly associated with the enigmatic *neglect* syndrome. Here the patient is apparently unaware of the existence of objects/events in the hemispace contralateral to the damage. Such individuals cannot identify stimuli in the contralesional field, nevertheless they are able to make same-different judgements regarding stimuli presented simultaneously to the contralateral and ipsilateral fields (Volpe & Gazzaniga, 1979). Thus neglect shares features of consciousness with the amnesic syndrome (Chapter 4) and blindsight. The notion that there can be a dissociation between the processing of information and conscious awareness is supported by studies demonstrating that such information can be manipulated at a semantic level by higher order priming, and that neglect impacts on visual memory of the patient's premorbid life (Bisiach & Luzzatti, 1978). Thus, as well as its involvement in the disengagement of attention, the parietal cortex (possibly restricted to the right superior portion) appears to be necessary for attending to and coding immediate internal and long-term representations of visual space.

5.   Neurochemistry

5.1 Non-specific effects

In examining the neurochemical machinery of attentional systems, the present section is largely restricted to apparently selective effects of drugs targeting various neurotransmitter systems. First it is worth briefly considering less specific effects. For example, in primates, injections into the medial region of the lateral pulvinar of the GABA-ergic agonist (muscimol) and antagonist (bicuculine) impair and facilitate covert attentional shifting respectively (Peterson et al., 1987; Robinson & Peterson, 1992). Similarly, in humans, there is evidence of attentional impairment from the administration of benzodiazepines (Koelega, 1989; Hindmarch & Tiplady, 1994). However it seems likely that such effects are due to interactions with executive GABA-ergic systems (see Chapter 1) rather than specific modulation of attentional processes. Similarly it is clear that attention may be compromised during alcohol intoxication. The subjective state of alcohol intoxication is similar to that induced by nitrous oxide and by hyperbaric nitrogen ('rapture of the deep'). These effects are most readily attributed to the drugs' CNS depressant activity, due either to generalised decreases in cortical arousal arising from non-specific membrane stabilisation (Tiplady, 1995),
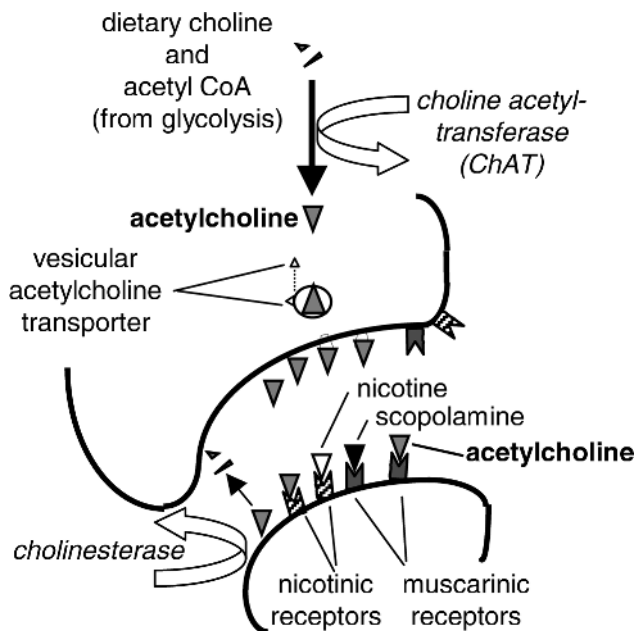
Figure 5. Cartoon of a cholinergic synapse showing major steps in the synthesis of acetylcholine. The two major receptor types, the ionotropic nicotinic receptor and the metabotropic muscarinic receptor, are shown (see also Chapter 1). Presynaptic muscarinic (M2) and nicotinic receptors are also depicted. Drugs which have been widely used to manipulate the cholinergic systems, and which are mentioned in the text, include the muscarinic receptor antagonists scopolamine and atropine and the nicotinic receptor agonist nicotine. Anticholinesterases (discussed elsewhere in this volume) include drugs such as physostigmine, rivastigmine, donepezil, and galanthamine.

or to more specific ionophore-ligand interaction (see Chapter 1). On the other hand there is some evidence that alcohol has more effect on tasks of divided attention (Wallgren & Barry, 1970) than those requiring simpler psychomotor attentional processing (Moskowitz & Sharma, 1974; Moskowitz, 1984).

The following section will consider the role of four neurotransmitter systems specifically implicated in attention. Concentrating on the cholinergic and noradrenergic mechanisms, it will also briefly consider dopaminergic and serotonergic systems. The synthetic pathways of each are presented schematically in figures (Figs 5, 6 and 7). The major neuroanatomical pathways of each are detailed clearly in Chapter 1 and in other chapters, and the following sections should be viewed particularly in relation to the distribution of receptor subtypes described therein.

5.2 Acetylcholine

More than any other neurotransmitter, acetylcholine has been implicated in attentional processes and in consciousness (Perry et al., 1999). Muscarinic blockade by scopolamine (Figure 5) results in a state of consciousness described as "twilight sleep" and results in impaired performance on a number of attentional measures. The Rapid Visual Information Processing (RVIP) task (see Sec. 2.4) has provided a prototypical paradigm for assessing the effects of cholinergic manipulation on sustained attention. Scopolamine administration impairs RVIP task performance—this decrement is reversed by nicotine administration, which itself enhances task performance (Wesnes & Revell 1984; Wesnes & Warburton 1884; Foulds et al., 1996). The cholinergic system has similarly been implicated in performance of a range of attentional tasks including the Stroop paradigm. Nicotine administration has been shown to improve performance on 'intensity' features of attention (Sec. 2.3), as measured by increased speed of performance in a number generation task, and of processing speed in both congruent and incongruent trials of the Stroop paradigm (Mancuso et al., 1999). Of around a dozen published studies into the effects of nicotine on Stroop performance, roughly half have reported no effect, four reported faster response times to name colours but not the Stroop effect itself, and two have found a reduction in the Stroop effect. Such results are broadly consistent with the view that nicotine improves intensity rather than selectivity of attention. Additionally, P300 latency is reduced following nicotine administration (Edwards et al., 1985) suggesting more efficient processing of stimuli, this measure has been identified as a correlate of conscious processing (see Chapter 1 and Perry et al., 1999).

With reference to divided attention, an association has been reported between blood glucose levels and performance on effortful dichotic listening paradigm (Parker & Benton, 1995). While similar effects have been attributed to acetylcholine precursor (acetyl CoA) synthesis linked to glucose metabolism (Wenk, 1989), it is also possible that simple provision of metabolic substrates may account for such findings (Kennedy & Scholey, 2000).

Cholinergic antagonism by scopolamine slows reaction times to invalidly cued targets more than to validly cues targets during the covert cueing paradigm (Cockle & Smith 1996). In an adaptation of the task, using exogenous cues, nicotine administration reduced the disadvantage of invalid cueing (Murphy & Klein, 1998). This it appears that increased cholinergic activity facilitates the disengagement of attention towards a cued location.

The quote from William James cited in the introduction continues "Focalisation, concentration of consciousness are of it essence. It implies *withdrawal from some things in order to deal effectively with others*" (italics added). While the measures of attentional 'focalisation' described above appear to benefit from increased cholinergic activity, there are reports of an opposite effect for tasks which assess 'broadened' attention, which might be described on James' terms as requiring cognitive "withdrawal from some things." One example is a task measuring the extent of cognitive flexibility, or ability to release from mental 'Set'. The capacity to adopt a new more efficient rule in an a series of algebraic problems, the Estellung Water Jars task, is enhanced by administration of the cholinergic antagonist atropine (Callaway & Band, 1958), and preliminary results suggest that it may be impaired by nicotine administration (Scholey et al., 1998). Such findings suggest a critical role for cholinergic activity in focussing attention.

The above pharmacological manipulation of attentional measures by cholinergic agents can be explained in part by changes in the activity of the basal forebrain cholinergic system which constitutes the major cholinergic input to the neocortex (see Chapters 1 and 2). These projections include posterior parietal and frontal lobe targets which contribute to a distributed network that also includes thalamic and other subcortical nuclei involved in the control of attention (Chapter 1). Such a system may impose cortical desynchronisation which optimises efficient attentional stimulus processing, affecting intensity features of attention while having a negligible or even negative effect on selectivity features (Mancuso et al., 1999).

Lesions of the basal forebrain cholinergic system using α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA) result in impaired attentional, but not mnemonic, function in rats (Muir et al., 1995) and monkeys (Voytko et al., 1994), an effect which has been confirmed using more selective IgG-saporin lesions (Baxter et al., 1995; Everitt & Robbins, 1997).

There is a growing consensus that attentional deficits in Alzheimer's disease may be as, or even more, important than mnemonic impairments. There is also evidence that cholinergic drugs may preferentially target such deficits. Furthermore the fluctuating, second-by-second 'stalling' of consciousness observed in dementia with Lewy bodies may be associated with temporal and cingulate cortex cholinergic deterioration (Chapter 14). The extent to which such phenomena may be related to lapses in attention or consciousness (e.g. microsleeps) in non-pathological populations is not known at present.

5.3 Noradrenaline

The noradrenergic system plays a crucial role in attentional orientation (reviewed by Coull, 1998). Imaging studies suggest that a noradrenergic network comprising frontal, parietal and thalamic structures may mediate attentional performance. The noradrenergic drug clonidine (Fig. 6) diminishes the cost of invalid cueing in covert orientation paradigms, while leaving the effect of valid cueing unaffected (Clark et al., 1989). Thus it appears that a reduction in noradrenaline normally facilitates disengagement of spatial attention. Conversely the α_2 antagonist idazoxan reduces 'inhibition of return' (or 'inhibitory after effect') where, with a relatively long interstimulus interval (>300 msec), response times are slowed to stimuli presented in the same spatial location as immediately previous presentations. Here increasing noradrenaline levels appears to reduce the selection of responses favouring novelty (which presumably acts to optimise visual sampling). Clonidine administration also results in reduced accuracy, particularly in familiarised subjects, on the Rapid Visual Information Task which assesses non-spatial sustained attention (see 2.4). That is decreasing noradrenaline levels impairs the ability to select and update semantic structures during such processing. Similar deficits are observed in individuals with frontal lobe damage (see Coull, 1998). Such findings are consistent with the notion that a frontal noradrenaline system enables focussed attention by attenuating the effects of distracters (Robbins, 1986; Coull, 1998), an effect which may be less evident under conditions of heightened arousal. Thus lesions of the dorsal noradrenergic ascending bundle (DNAB) in rats impairs accuracy and response times on a five-choice serial reaction time task only during conditions of heightened arousal—i.e. during a random interstimulus interval or in the presence of white noise (Carli et al., 1983). Witte and Marroco (1997) examined the effects of administration of clonidine and guanfacine (another α_2 agonist) on a covert orientation task in monkeys. No effect was found regarding invalid cueing but noradrenaline blockade reduced the advantage of receiving a neutral (non-orienting) cue compared with no cue. Again these data support a role for noradrenaline in alerting/arousal rather then attention *per se*. It appears then that noradrenaline may be involved in the control of 'bottom-up' modulation of attention.
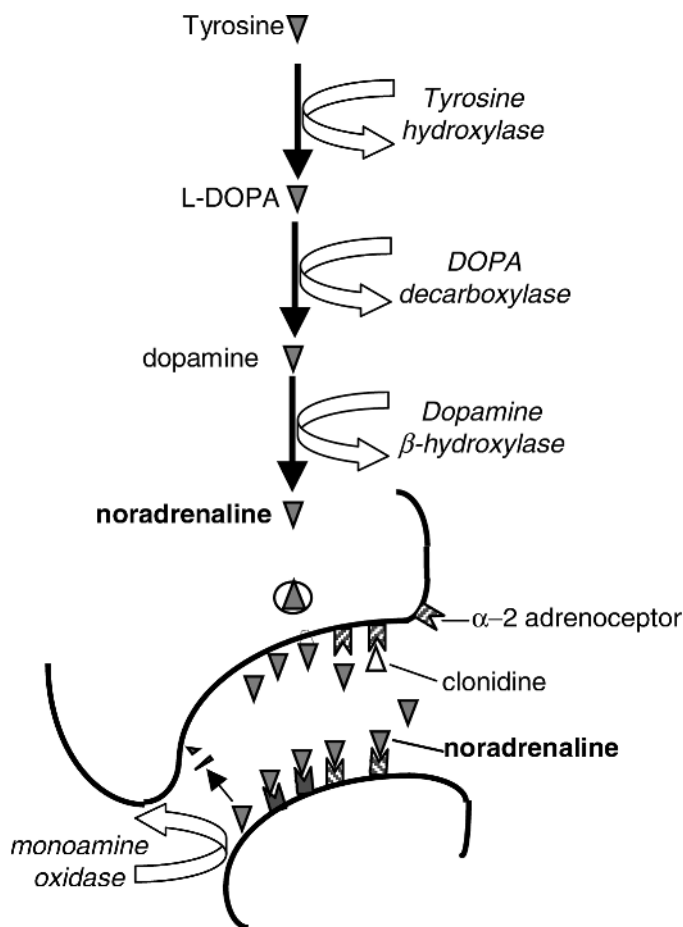
Figure 6. A noradrenergic synapse. Synthetic steps involved in the production of nora-drenaline are depicted. In dopaminergic synapses these do not proceed beyond the pro-duction of dopamine which, following release, binds receptors including the D1 and D2 receptors (see text). In noradrenergic synapses, dopamine is converted to noradrenaline by the action of dopamine β-hydroxylase. Actions of the noradrenergic agent clonidine include activation of (inhibitory) presynaptic alpha-2 (α-2) adrenoceptors, effectively down-regulating central noradrenergic activity (activation of postsynaptic α-2 recep-tors generally has opposite effects). Other key postsynaptic receptors include the alpha-2 and beta-1 adrenoceptors. Manipulation of the noradrenergic system also occurs via the actions of monoamine oxidase inhibitors (discussed elsewhere) which can be cate-gorised as 'classical' — non-selective and irreversible (e.g. phenelzine, tranylcypromine, isocarboxazid), reversible (moclobemide), or selective (deprenyl).

5.4 Dopamine

The effects of dopamine on simple attentional processing are less clear. However dopaminergic pathways do seem to play a pivotal role in aspects of shifting attention. 6-hydroxydopamine lesioned animals exhibit impaired delayed recall but improved set-shifting performance. Conversely set-shifting is impaired by the D1/D2 antagonist haloperidol (Berger et al., 1989), as is Stroop performance (Williams et al., 1997)—while aspects of focussed attention remain relatively spared. Such findings have been attributed to reduced prefrontal and consequent increased striatal dopamine levels (Brozowski et al., 1979). These effects may be due to activity within a dopaminergic pathway which subserves a 'lower' (tonic) arousal system. In this model an 'upper' (phasic) noradrenergic arousal system is involved in response selection (Robbins, 1984; 1997; Elliot et al., 1997). In situations of heightened arousal, such as processing in situations of novelty, the 'upper' NA system is activated, while in situations relying on attentional processing only the 'lower' system is required. Thus administration of the DA agonist methylphenidate decreases performance only when subjects are familiar with a task (Elliot et al., 1997). This result has been attributed to overloading of the 'lower' system by surplus DA, coupled with an absence of activation of the 'higher' system (this due to familiarisation with the task). Rewarding stimuli are more arousing than neutral ones, and the role of DA in such effects is considered in Chapter 5.

5.5 Serotonin

One method which has been proved fruitful in manipulating the serotonergic system is acute tryptophan depletion (ATD—see Figure 7). This method exploits the fact that the serotonergic precursor tryptophan and other large neutral amino acids (LNAAs) compete for the same blood-brain barrier transporter system. Since levels of tryptophan are rate-limiting for serotonin synthesis drinking a LNAA-minus-tryptophan cocktail effectively restricts central serotonin synthesis to approximately one tenth its normal rate (Nishizawa et al., 1997). It is reasonably well established that ATD impairs memory consolidation within 30 minutes of learning target material (e.g. Reidel et al., 1999; Schmitt et al., 2000). Conversely, focussed attention appears to be enhanced by serotonin depletion. Following ATD, subjects show speeding of responses, apparently due to an attenuation of stimulus-response incongruity (Coull et al., 1995), including a less pronounced Stroop effect (Rowley et al., 1997; Schmitt et al., 2000) and the ability to focus on one stimulus stream in a dichotic lis-
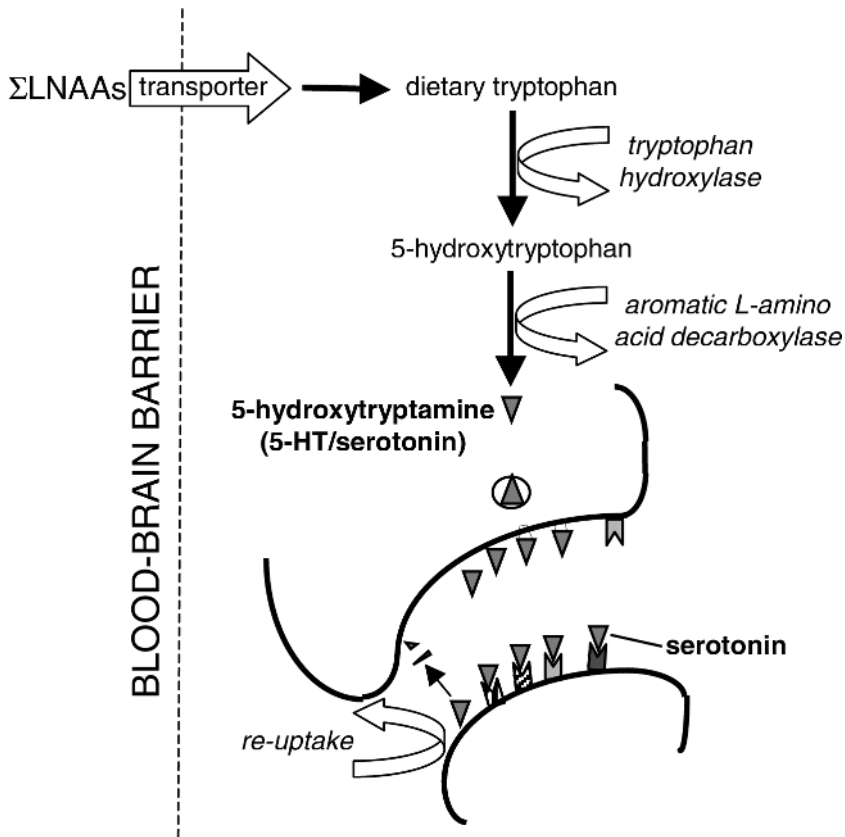
Figure 7. A serotonergic synapse including a depiction of the acute tryptophan depletion method discussed in the text. All large neutral amino acids (ΣLNAAs) share a common blood-brain barrier transporter. The serotonergic precursor, tryptophan, essentially competes with the other LNAAs for transport. Thus tryptophan is uniquely susceptible to acute dietary manipulation. Numerous serotonergic receptor types exist, including presynaptic 5-HT$_{1D}$ and (somatodendritic) 5-HT$_{1A}$ autoreceptors and postsynaptic 5-HT$_{1A}$, 5-HT$_{1D}$, 5-HT$_{2A}$, 5-HT$_{2C}$, 5-HT$_3$ and 5-HT$_4$ receptors. Additional modulation of serotonin activity can occur via the action of selective serotonin re-uptake inhibitors (SSRIs) including fluoxetine, fluvoxamine, and citalopram.

tening paradigm (Schmitt et al., 2000). While these effects are certainly not restricted to the attentional domain they do suggest a role for serotonin reduction in narrowing the focus of attention.

Conclusion

The above discussion has been restricted to experimental dissociation of implicitly distinct neural substrates, providing a useful heuristic by which to begin to untangle the neurochemical substrates of attention. It is worth noting that rich and reciprocal interactions exist between monoaminergic (and other) neurotransmitters. Investigation into these interactions will be necessary in order to obtain a fuller picture of the necessary, sufficient and exclusive neurochemical mechanisms of attention.

References

Allport, A. (1993). In Meyer, D. & Kornblum, S. (Eds.), *Attention and performance XIV: a silver jubilee* (183–218). Cambridge MA: MIT Press.

Baddeley, A. (1995). In Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences*. Cambridge MA: MIT Press, pp. 755–764.

Behrmann, M. & Tipper, S.P. (1994). In Ulmilta, C. & Moscovitch, M. (Eds.), *Attention and performance XV: conscious and nonconscious information processing* (351–375). Cambridge MA: MIT Press.

Berger, H.J.C. et al. (1989). *Neuropsychologia* 27, 629–639.

Bisiach, E. & Luzzatti, C. (1978). *Cortex* 14, 129–133.

Broadbent, D.E. (1958). *Perception and Communication.* New York: Pergamon Press.

Broadbent, D.E. (1971). *Decision and Stress.* New York: Academic Press.

Brozoski, T.J. et al. (1979). *Science* 205, 929–931.

Callaway, E. & Band, R.I. (1958). *J. Neurol. Psychiatr.* 79, 91–102.

Cherry, E.C. (1953). *Journal of the Acoustic Society of America* 25, 975–979.

Clark, C.R. et al. (1989). *Neuropsychologia* 27, 131–139.

Cockle, S.M. & Smith, A.T. (1996). *Perception* 25, S140.

Coles, M.G.H. et al. (1995). In Rugg M.D. & Coles M.G.H. (Eds.), *Electrophysiology of Mind: Event-related brain potentials and cognition* (86–131). Oxford: Oxford University Press.

Corbetta, M. et al. (1991). *Journal of Neuroscience* 11, 2383–2402.

Corbetta, M. et al. (1993). *Journal of Neuroscience* 13, 1202–1226.

Corbetta, M. et al. (1995). *Science* 270, 802–805.

Coull, J.T. (1998). *Progress in Neurobiology* 55, 343–361.

Coull, J.T. et al. (1995). *Psychopharmacology* 121, 222–230.

Crick, F. (1992). In Kosslyn, S.M. and Anderson, R.A. (Eds.), *Frontiers in Cognitive Neuroscience* (366–372). Cambridge MA: MIT Press.

Dennett, D. (2001). *Cognition* 79, 221–237.

Donchin, E. & Coles, M.G.H. (1988). *Behavioral Brain Sciences* 11, 355–372.

Edwards et al. (1985). *Addictive Behaviours* 10, 113–126.

Elliot, R. et al. (1997). *Psychopharmacology* 131, 196–206.

Everitt, B.J. & Robbins, T.W. (1996). *Annual Review of Psychology* 48, 649–684.

Foulds, J. et al. (1996). *Psychopharmacology* 127, 31–38.

Heinze, H.J. et al. (1994). *Nature* 372, 543–546.

Hillyard, S.A. et al. (1973). *Science* 182, 177–180.

Hillyard, S.A. et al. (1995). In Gazzaniga, M.S. (Ed.), *The Cognitive Neurosciences* (665–681). Cambridge MA: MIT Press.

Hindmarch, I. & Tiplady, B. (1994). *Human Psychopharmacology* 9, 43–49.

James, W. (1890). *Principles of Psychology*. New York: H.Holt.

Kennedy, D.O. & Scholey, A.B. (2000). *Psychopharmacology* 149, 63–71.

Koelega, H.S. (1989). *Psychopharmacology* 98, 145–156.

LaBerge, D. (1990). *Journal of Cognitive Neuroscience* 2, 358–372.

Mancuso, G. et al. (1999). *Psychopharmacology* 146, 199–204.

Moran, J. & Desimone, R. (1985). *Science* 229, 782–784.

Moskowitz, H. & Sharma, S. (1974). *Human Factors* 16, 174–180.

Moskowitz, H. (1984). *British Journal of Clinical Pharmacology* 18, 51–61S.

Mountcastle, V.N. (1976). *Neuroscience Research Progress Bulletin* 14S, 1–47.

Muir, J.L. et al. (1995). *Psychopharmacology* 118, 82–92.

Murphy, F.C. & Klein, R.M. (2000). *Neuropsychologia* 36, 1103–1114.

Nishizawa, S. et al. (1997). *Proceedings of the National Academy of Sciences USA* 94, 5308–5313.

Norman, D.A. & Shallice, T. (1986). In Davidson, R.J., Schwartz, G.E. & Shapiro, D. (Eds.), *Consciousness and Self Regulation, Vol. 4* (1–18). New York: Plenum Press.

Parasuraman, R. et al. (1993). *Neuropsychology* 7, 242–272.

Parasuraman, R. (1984). In Warm, J.S. (Ed.), *Sustained Attention in Human Performance* (61–101). Cambridge: John Wiley.

Parker, P.Y. & Benton, D. (1995). *Neuropsychologia* 33, 843–854.

Perry, E.K. et al. (2000). *Trends in Neuroscience* 22, 273–280.

Perry, R.J. & Hodges, J.R. (1999). *Brain* 122, 383–404.

Peterson, S.E. et al. (1987). *Neuropsychologia* 25, 97–105.

Peterson, S.E. et al. (1992). *Current Opinion in Neurobiology* 2, 217–222.

Posner, M. (1994). *Proceedings of the National Academy of Sciences USA* 91, 7398–7403.

Posner, M.I. & Peterson, S.E. (1990). *Annual Review of Neurosciences* 13, 25–42.

Posner, M.I. et al. (1984). *Journal of Neuroscience* 4, 1863–1874.

Rafal, R. & Posner, M.I. (1987). *Proceedings of the National Academy of Sciences USA* 84, 7349–7353.

Reidel, W.J. et al. (1999). *Psychopharmacology* 141, 362–369.

Robbins, T.W. (1984). *Psychological Medicine* 14, 13–21.

Robbins, T.W. (1997). *Biological Psychology* 45, 57–71.

Robinson, D.L. & Peterson, S. (1992). *Trends in Neuroscience* 15, 127–132.

Rowley, B. et al. (1997). *Journal of Psychopharmacology* 11, A60.

Schmitt, J.A.J. et al. (2000). *Journal of Psychopharmacology* 14, 21–29.

Scholey, A.B. et al. (1998). *Journal of Psychopharmacology* 12, A45.

Stroop, J. (1935). *Journal of Experimental Psychology* 18, 643–662.

Tiplady, B. (1995). In Hindmarch, I. & Stonier, P.D. (Eds.), *Human Psychopharmacology, Vol. 5* (89–109). Chichester: John Wylie & Sons Ltd.

Treisman, A.M. (1964). *Psychological Review* 76, 282–299.

van Zomeren, A.H. & Brouwer, W.H. (1994). *Clinical Neuropsychology of Attention.* Oxford: Oxford University Press.

Volpe, B.T. et al. (1979). *Nature* 282, 722–724.

von Hemholtz, H. (1894). *Handbuch der Physiologischen Optik.* Leipzig: L. Vos., Hamburg.

Voytko, M.L. et al. (1994). *Journal of Neuroscience* 14, 5986–5995.

Wallgren, H. & Barry, H. III (1970). *Actions of Alcohol.* New York: Elsevier.

Wenk, G.L. (1989). *Psychopharmacology* 99, 431–438.

Wesnes, K.A. & Revell, A. (1984). *Psychopharmacology* 84, 5–11.

Wesnes, K.A. & Warburton, D.M. (1984). *Psychopharmacology* 82, 147–150.

Williams, J.H. et al. (1997). *Journal of Psychopharmacology* 11, 247–252.

Woldorff, M.G. et al. (1993). *Proceedings of the National Academy of Sciences USA* 90, 8722–8726.

Wurtz, R.H. et al. (1982). *Scientific American* 246, 124–135.

Yingling, C.D. & Skinner, J.E. (1976). *Electroencephalography and Clinical Neurophysiology* 41, 476–482.

Chapter 4

Memory

Caroline Stewart

1. Consciousness and memory

There are many definitions of consciousness but most agree with William James (1990) that it includes awareness of oneself (or one's own cognitive experience) and the environment. In terms of the underlying neurobiology, consciousness has been described as an active process requiring the cooperation of multiple brain circuits involved in alertness, attention, executive function, awareness, sensation/perception, explicit memory and motivation (Young and Pigott, 1999). Memories are the representations of acquired knowledge and skills during a lifetime. They are an essential part of a person's individuality, a record of past experiences that can be consciously recalled or re-lived.

Memory has been subdivided into different psychological sub-systems, some of which are linked to conscious awareness. One of the most enduring distinctions made is between explicit (or declarative) and implicit (or procedural) memory. Explicit memory, such as occurs for specific events or facts, is revealed when tasks require conscious recollection (Squire, 1986). It is the highest form of memory, a phylogenetically recent capacity, and allows an individual to relate past experiences to the present and also to the future. Implicit memory, for certain learned psychomotor or perceptual skills for example, occurs without conscious awareness. The inability to store or recall explicit memories, as occurs in amnesia, does not lead to an overall loss of consciousness as the other participating components, for example attention and general awareness, are preserved. However there is no doubt that profound amnesia is severely debilitating and Young and Pigott (1999) describe it as the loss of "an important component of mental activity that allows the conscious linking of the past and present." This process of conscious recollection is probably occurring constantly in normal individuals providing a sense of familiarity and continuity. Sufferers of dense amnesia are essentially trapped in a time period

before the amnesia began. They cannot move forward as they are unable to lay down and access any new memories.

2.   Neuroanatomy of memory

The determination of specific brain structures involved in the formation of memories has been guided by the study of human amnesics and by attempting to replicate features of the human amnesic syndrome using lesion studies in animals. Overall analysis of the pathology found in amnesia (Squire, 1986) suggests that damage occurs either to diencephalic brain regions (thalamus, mammillary bodies) or to the medial temporal lobe (hippocampus, amygdala). Characteristically, damage to these areas produces an anterograde amnesia (difficulty in learning and remembering new material) and a variable retrograde amnesia (failure to recall events occurring prior to the onset of amnesia).

General intellectual function, language and short-term memory function are usually intact in amnesic patients. There is evidence that some degree of residual learning capacity, particularly for tasks relying on implicit or procedural memory such as psychomotor skills, is also spared. The fact that memory for the remote past is often undamaged indicates that long-term storage does not occur in the medial temporal and diencephalic brains areas implicated in amnesia. Immediate or short-term memory is also independent of these regions and may be an intrinsic capacity of each cortical processing system (visual, auditory, etc.). Priming effects, the influence of behaviour by recent exposure to stimulus material, may also depend exclusively on cortical representations (Squire, 1986).

It has been difficult to determine the minimum lesions required to produce amnesia as patient groups differ in both their neuropsychological function and the aetiology and neuropathology of their condition. Amnesia can occur as a consequence of a variety of brain insults: traumatic head injury, tumours, encephalitis, strokes, surgery, electroconvulsive therapy and chronic alcohol abuse. However, severe anterograde amnesia with limited retrograde amnesia has been seen following a very discrete lesion to the CA1 cell field of the hippocampus caused by an ischaemic episode (Zola-Morgan et al., 1986). The hippocampus has therefore been considered as the core brain structure for conscious memory, perhaps acting as the "gateway" for awareness to enter into memory (Eichenbaum, 1999). A recent study by Chun and Phelps (1999) suggests that the hippocampus can also mediate some forms of implicit or un-

conscious learning concerning the relationship of context with cue presenta-
tions. Eichenbaum (1999) suggests that the primary role of the hippocampus
is to mediate the networking of memories and conscious awareness will require
the involvement of this hippocampal network although some memories can be
networked without it.

Temporal lobe brain structures, in particular the hippocampal formation,
appear to play a pivotal yet transient role in the formation of new explicit mem-
ories. This chapter focuses on possible neurochemical mechanisms underlying
the encoding of new information in the hippocampus and the modulation of
memory function by different neurotransmitter systems in the brain.

3.   Neurochemistry of memory

3.1   The synaptic model

An early theoretical model for associative learning was proposed by Donald
Hebb (1949), even before the existence of the synapse had been demonstrated:
"when an axon of a cell A is near enough to excite a cell B and repeatedly and
persistently takes part in firing it, some growth process or metabolic change
takes place in one or both cells such that A's efficiency, as one of the cells firing
B, is increased." This strengthening process would allow the co-occurrence of
neuronal events to be recorded in networks of neurons that could then be used
as the building blocks for memory representations in the brain. The Hebb rule
is just one principle that has been used in the development of artificial neural
networks. The ability to store complex information is also a function of the
network architecture or the pattern of neuronal connections in the network
(see Jeffery and Reid, 1997).

3.2   Long-term potentiation

The discovery by Bliss and colleagues of an electrophysiological phenomenon
known as long-term potentiation (LTP) provided a plausible neural candidate
for Hebbian-style learning (Bliss and Lomo, 1973). LTP is a long-lasting in-
crease in the extra-cellular response of a neuronal population in the rabbit
hippocampus (Fig. 1A) brought about by applying trains of high frequency
stimulation to the afferent pathway (Fig. 1B). Prior to this discovery, most
neurophysiological phenomena that could be demonstrated in the brain were
relatively short-lived and in some cases non-specific. LTP represented a form
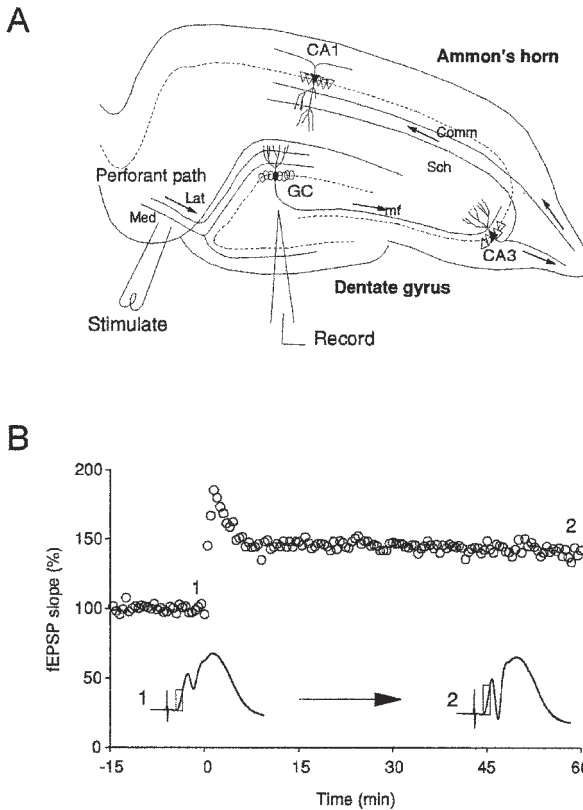
A

B

Figure 1. A. Simplified diagram of the rodent hippocampal formation illustrating the major glutamatergic circuitry. The principal neuronal fields: granule cells (GC) of the dentate gyrus and pyramidal cells of CA1 and CA3 in Ammon's horn are shown. The main excitatory connections are also indicated: the perforant path from entorhinal cortex to the granule cells, from there the mossy fibre (mf) axonal projections to CA3 and then the Schaffer collaterals (Sch) from CA3 to ipsilateral CA1 and commissural (Comm) to contralateral CA1 cells. Evoked responses in (B) were obtained by stimulating the afferent pathway from entorhinal cortex, the medial perforant path (Med), and recording the granule cell (GC) response in the hilus of the dentate gyrus.
B. Long-term potentiation in the dentate gyrus recorded in vivo. The graph plots the early rising slope of the field excitatory postsynaptic potential (EPSP) in response to low frequency stimulation (700 μA, 100 ms, 0.05 Hz). Four trains of high frequency stimulation (700 μA, 82.5 ms, 400 Hz) were delivered at time 0. This produced an immediate increase in the EPSP slope (post-tetanic potentiation) and a sustained relatively constant enhancement that lasted for at least 60 minutes. Representative traces are included below the graph. Note the obvious increase in size of the superimposed population spike (downward deflection).

of synaptic plasticity that was rapidly established, durable and specific only to the inputs stimulated. These were characteristics considered essential for any neural mechanism proposed to underlie memory formation (Bliss and Collingridge, 1993; Maren and Baudry, 1995). Long-term depression (LTD) is a lasting activity-dependent decrease in synaptic efficacy that can also be induced in the hippocampal formation using different induction protocols (e.g. Staubli and Scafidi, 1997). The fact that synaptic weights could be both downregulated and upregulated was used to improve the accuracy of memory recall in associative matrix models (Willshaw and Dayan, 1990).

3.3 Glutamatergic transmission and the NMDA receptor

LTP has been demonstrated in several areas of the mammalian brain including the amygdala (Clugnet & LeDoux, 1990) and the neocortex (Laroche et al., 1990). It has also been shown to occur in the human hippocampal dentate gyrus (Beck et al., 2000). Excitatory amino acids are the neurotransmitters responsible for transmission at most of the synapses that exhibit LTP. The most widely studied, and probably most abundant form of LTP requires activation of a specific sub-class of excitatory amino acid (EAA) receptor, the N-methyl-D-aspartate (NMDA) receptor, for its induction (Collingridge et al., 1983). This receptor is a complex molecular entity with a five-subunit structure, consisting of numerous ligand binding sites and an integral ion channel (Fig. 2). The ion channel is both ligand- and voltage-gated. Current flow through the channel is prevented at resting membrane potential by magnesium ion blockade and normal synaptic transmission is usually mediated by the flow of cations (mainly sodium) through AMPA-receptor related ion channels (Collingridge et al., 1983). When the post-synaptic membrane is sufficiently depolarised, the magnesium block is released, allowing sodium and calcium ions to enter through the NMDA-receptor associated channel in the presence of glutamate. This dual requirement for both ligand activation (presynaptic activity resulting in glutamate release) and sufficient membrane depolarisation (postsynaptic activity) allows the NMDA receptor to detect the co-incident pre and postsynaptic events as defined by Donald Hebb (1949).

3.4 Other factors affecting LTP induction

The fact that LTP induction requires both ligand binding to the NMDA receptor, and sufficient depolarisation of the postsynaptic membrane, means that factors affecting either process will have an impact on whether LTP is ob-
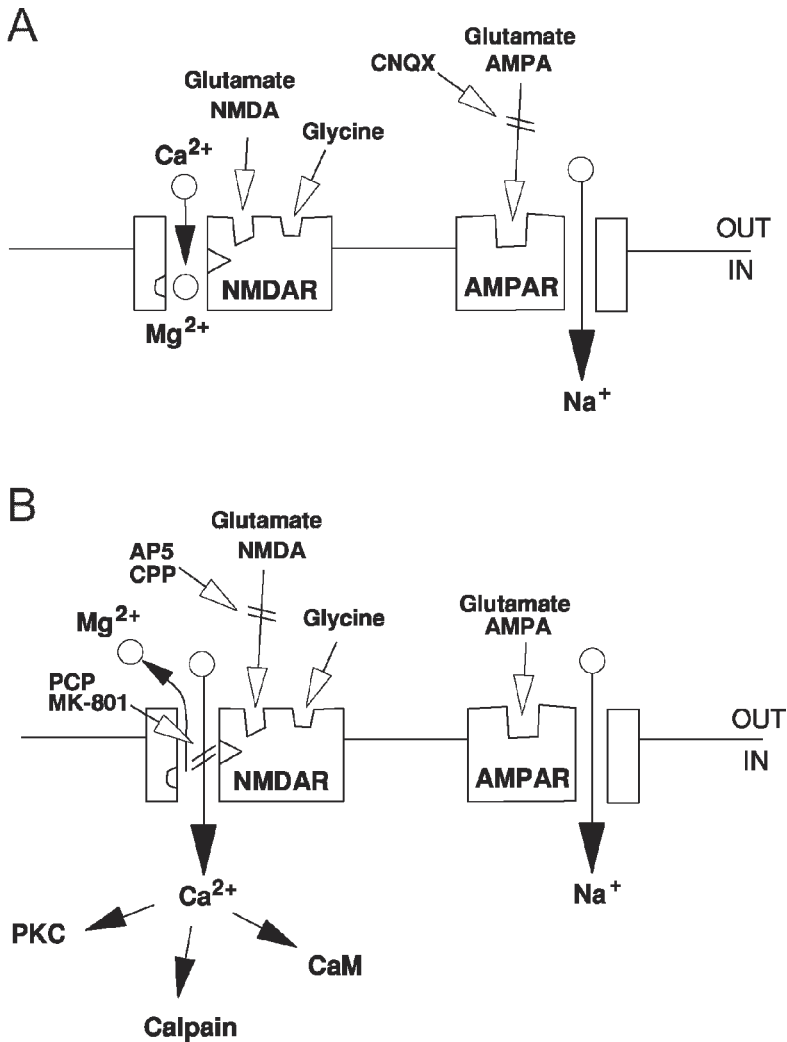
Figure 2. The neurochemistry of NMDA-dependent LTP induction. A. During low frequency stimulation the field EPSP displayed in Figure 1B is mediated predominantly by L-glutamate acting on non-NMDA (e.g., AMPA) receptors. This can be blocked by the competitive antagonist 6-cyano-7-nitroquinoxaline-2,3-dione (CNQX). NMDA receptor activity is blocked by Mg^{2+} in the ion channel. B. During high frequency activation the postsynaptic cell becomes depolarised and in the presence of L-glutamate Ca^{2+} ions can enter through the receptor associated ion channel. NMDA receptor activity, and therefore LTP, can be blocked by either competitive (AP5, CPP) or non-competitive (PCP, MK-801) antagonists. Ca^{2+} entry into the neurone may result in expression of LTP through a variety of second messenger molecules.

tained. During low frequency stimulation, the magnesium block sustained by postsynaptic hyperpolarisation, the level of which can be controlled by gamma amino butyric acid (GABA)-mediated synaptic inhibition, prevents activation of NMDA receptors. During high frequency stimulation there is fatigue of synaptic inhibition due to GABA inhibiting its own release through activation of $GABA_B$ autoreceptors "allowing" LTP to be induced. Selective antagonists at the $GABA_B$ receptor can therefore block the induction of high frequency-induced LTP (Davies et al., 1991) whereas agonists can facilitate it (Mott et al., 1990). There is also some evidence that metabotropic glutamate (mGlu) receptors, a family of G-protein linked excitatory amino acid receptor, can control the induction of LTP. The action of mGlu receptor activation has been described as being like a molecular switch (Bortolotto et al., 1994). Once activated, for example by application of the mGlu receptor agonist ACPD, LTP becomes insensitive to blockade by an mGlu receptor antagonist MCPG. Not all studies have managed to replicate blockade of LTP by MCPG, nor the action of mGlu receptors as a molecular switch and it is possible that effects are only seen during specific experimental conditions (Wilsch et al., 1998).

Identical experimental stimulation paradigms do not always result in successful LTP. Prior electrical stimulation of the Schaffer collateral to CA1 pathway that did not itself induce LTP nonetheless inhibited LTP induction by subsequent tetanic stimulation (Huang et al., 1992). This inhibition of future LTP was prevented if an NMDA receptor antagonist (AP5) was present during the initial stimulation. These types of "priming" stimuli may in fact enhance the chances of obtaining LTD (Christie and Abraham, 1992). Alteration in the degree of synaptic enhancement or in the direction of change in synaptic efficacy to a given stimulus train has been termed metaplasticity (Abraham and Bear, 1996). This property allows previous experience (represented experimentally by patterns of stimulation) to affect the probability of obtaining LTP or LTD in a neural circuit at a later date. In terms of a neural network this property has been described in the Bienenstock-Cooper-Munro (BCM) model as θm or the "modification threshold" that facilitates bi-directional change (described in Kim and Yoon, 1998 and Martin et al., 2000).

3.5 Mechanisms of LTP expression

The calcium current through the NMDA receptor related ion channel becomes the signal that co-incident events have been detected (Lynch et al., 1983) and activates further intracellular pathways. Several potential transduction mechanisms could lead to the long-term expression of LTP including the protease cal-

pain, phosphatases and protein kinases (protein kinase C, calcium/calmodulin dependent protein kinase II and cAMP dependent protein kinase A). Sanes and Lichtman (1999) reviewed these and many other molecular entities that have been implicated somehow in the mechanisms underpinning LTP and LTD. They suggest that there can be a problem in distinguishing between mediators (required agents for LTP) and modulators (can alter the process but are not required for its occurrence).

There is still no consensus on the exact mechanism that leads to the maintenance or long-term expression phase of LTP (Bliss and Collingridge, 1993). It could be an increase in neurotransmitter release from the presynaptic terminal, an increase in the number or sensitivity of postsynaptic receptors, or morphological changes at the post-synaptic site. Modification of neuronal structure suggests a requirement for new protein synthesis in the late or maintenance phase of LTP. In the presence of certain protein kinases and phospholipase inhibitors, LTP-inducing stimulation produces a short-lasting synaptic enhancement that decays back to baseline in approximately 20 minutes (e.g. Colley et al., 1990). Within this time-window, LTP remains vulnerable and can be reversed ("de-potentiated") by several interventions including patterns of electrical stimulation (Hesse and Teyler, 1976; Fujii et al., 1991) and brief cooling (Bittar and Muller, 1993).

These observations may relate to the theoretical construct of memory consolidation (McGaugh, 1966). Memories do not become permanently fixed at the moment of learning but some will stabilise with the passage of time and others will be degraded. Cognitive studies on the effects of electroconvulsive stimulation in both humans and other species suggested that more recent memories were more vulnerable to the amnesic effects of the treatment than remote memories, i.e. there was a temporal gradient for retrograde amnesia (Squire, 1986). The precise time-course during which memory consolidation occurs and the mechanisms responsible are not yet clear. Memories may require later reactivation in order to strengthen or reorganise the original representations to allow the addition of new information. Some studies described in a review by Sara (2000) suggest it is not necessarily recent memories, but reactivated memories that are susceptible to disruption by amnesic agents.

3.6 Experimental evidence for involvement of hippocampal LTP in memory formation

In the years that followed the discovery of LTP as a candidate neural mechanism for the memory trace, innumerable studies sought to substantiate the

link between LTP, learning and memory. It is accepted by most who use the LTP phenomenon as the theoretical encoding mechanism that information would probably be stored as alterations in specific synaptic weights that would be distributed throughout a network of connections. This being the case, unless many synapses change during a learning experience the chances of seeing "natural" LTP as a result of new memory formation were slim. Much of the evidence produced has been correlative and the earliest studies examined LTP longevity in ageing animals. The retention of spatial memories over time was correlated with the decay rate of LTP. Older animals exhibited faster rates of forgetting and LTP decayed more quickly (Barnes and McNaughton, 1985). A recent *in vitro* study examined NMDA-dependent LTP in hippocampal tissue from patients with temporal lobe epilepsy. LTP was severely impaired in patients with a primary hippocampal seizure focus compared to patients with an extrahippocampal focus (Beck et al., 2000). Previous studies had found that verbal memory performance was reduced in this patient group (Helmstaedter et al., 1997).

Parameters of LTP in animals have been manipulated to examine the consequences for learning and memory. Morris and colleagues (1986) found that intracerebroventricular (icv) administration of the competitive NMDA receptor antagonist D-amino-5-phosphonopentanoic acid (D-AP5) interfered with both spatial learning, a task shown to be sensitive to lesions of the hippocampus (Morris et al., 1982), and hippocampal LTP in the rat. Since then, many others have reported deficits in learning tasks following either systemic or intracerebral application of several NMDA receptor antagonists (reviewed in Danysz et al., 1995). Hippocampal NMDA receptors also appear to be necessary for verbal learning in humans. Ketamine, a non-competitive NMDA receptor antagonist impaired recognition memory and reduced the event-related electrophysiological response to recognised words (Grunwald et al., 1999).

The exact nature of the deficit produced by NMDA antagonists and the interpretation of results has been questioned. It is difficult to ignore the possibility that sensorimotor impairment, however subtle, may mediate the apparent spatial learning deficit in rats (Keith and Rudy, 1990). The fact that animals exhibiting minimal LTP still demonstrate significant learning is also challenging (Bannerman et al., 1995).

An alternative approach to pharmacological blockade of LTP is to drive the level of synaptic plasticity to a theoretical maximum by repeatedly inducing LTP experimentally (often termed "saturation"). Experimental induction of maximal LTP occluded the formation of new spatial memories (McNaughton et al., 1986; Castro et al., 1989). There was mixed success in replicating these

studies (see Bliss and Richter-Levin, 1993), although this may have been due to insufficient saturation of LTP throughout the hippocampus (Moser et al., 1998). Electroconvulsive stimulation, a procedure known to impair memory in humans and other species, can occlude experimentally-induced hippocampal LTP in rats and impair spatial learning in the open-field watermaze (Reid and Stewart, 1997). More recently, Brun et al. (2001) showed that LTP induced in the dentate gyrus by stimulating fibres throughout the angular bundle with a multi-electrode array, disrupted the recall of recently acquired spatial information. This effect was blocked by systemic administration of the competitive NMDA receptor antagonist 3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid (CPP). Interestingly, although recently acquired memories were affected by high frequency stimulation (HFS), new place learning following LTP induction was not. The authors suggested that disruption to synaptic weights is sufficient to impair retention but that new spatial information can be encoded as long as there is the potential for further synaptic enhancement, indicated by residual LTP in the HFS group.

Manipulation of the genes involved in either the expression of LTP has also been used to determine the relationship between hippocampal synaptic plasticity and memory. Knockout studies were carried out initially and involved the targeted deletion of specific genes. Mice deficient in the alpha subunit of CaMKII kinase, a molecule that controls LTP induction, exhibited impaired LTP (Silva et al., 1992a) and spatial learning (Silva et al., 1992b). Many studies followed that suggested the absence of particular genes coding for proteins required for normal LTP resulted in learning and memory impairment. This global approach was not without problems. The gene of interest was absent throughout the brain (and in fact the entire organism) and may have had an important role in development. Even if the knockout did not prove fatal, it was possible that other systems compensated for absence of the target gene. Second generation knockouts allowed region and cell-type specific targetting of gene deletions. Mice with a specific deletion to the NMDAR1 receptor in the CA1 region show impaired spatial memory in the watermaze. They did not express LTP in the CA1 region, although dentate LTP was normally induced (Wilson and Tonegawa, 1997).

Martin et al. (1999) published a comprehensive review of behavioural studies that relate to a "synaptic plasticity and memory hypothesis." They assessed the involvement of activity-dependent plasticity in information storage within the brain using four formal criteria: detectability, mimicry, anterograde alteration and retrograde alteration. They argued that these criteria were met to varying degrees in the studies outlined and suggested that synaptic plasticity is

necessary, but perhaps not sufficient for memory formation. The mechanisms that underlie memory retrieval processes appear to be even less resolved (Sara, 2000), although by definition the proof that a memory actual exists can only be seen when it is recalled. Retrieval of memories must require some kind of neural activity being passed through an existing network to recreate the patterns of firing that constitute a memory. There is some evidence that intact hippocampal AMPA/kainate receptor function may be necessary for accurate retrieval (Riedel et al., 1999).

3.7 Neurochemical modulation of memory and LTP

The hippocampus has innumerable afferent and efferent connections to other brain structures both within the limbic system and beyond. There are receptors for many different chemical signals ranging from the "classical" neurotransmitters such as acetylcholine to steroid hormones and neurotrophic factors. Some of these receptors are located in the synapses that form the intrinsic hippocampal circuits and others are the targets of specific projection pathways from other brain areas. A comprehensive review of all neurotransmitter interactions relevant to function is not within the scope of this chapter. There are detailed reviews of modulation of neurochemical systems on place learning in the watermaze (McNamara and Skelton, 1993) or other limbic-system dependent tasks (Izquierdo and Medina, 1995) in animals. The effects of key neurochemical, other than NMDA channel-mediated, and environmental influences are discussed below.

3.8 Synaptic inhibition and GABA

Evidence that GABAergic transmission influences learning and memory processes is highlighted by the fact that benzodiazepines (BZ), agonists at a modulatory site on the GABA$_A$ receptor, that are used to treat anxiety, insomnia and seizures impair memory. BZ also affect spatial learning and memory animals (reviewed in McNamara and Skelton, 1993). Flumazenil, a BZ antagonist, can reverse these deficits. Interestingly, inverse agonists at the benzodiazepine site may enhance spatial learning. This evidence suggests that levels of inhibitory transmission can be modulated to enhance or reduce LTP induction in the hippocampus. Flunitrazepam, a BZ agonist, significantly reduces LTP in CA1 in vitro whereas methyl 6,7-dimethoxy-4-ethyl-β-carboline-3-carboxylate (DMCM) an inverse agonist are enhancing it (Seabrook et al., 1997). In the dentate gyrus, antagonism of GABA$_B$ receptor function both suppresses LTP in

the dentate gyrus in vivo and impair spatial learning in the watermaze (Brucato et al., 1996).

3.9 Cholinergic system

The cholinergic system has long been implicated in cognitive processes. An outline of cholinergic anatomy and its involvement in consciousness has been provided in Chapter 2. Post-mortem study of patients with Alzheimer's disease suggests that the loss of cholinergic markers in the basal forebrain and cortex correlates significantly with the degree of cognitive impairment. Specific deficits in conscious awareness is discussed in Chapter 14. Although attentional processes are probably also affected by the disease, the earliest impairments in these patients appear to be for episodic memory (a type of explicit memory that relates to specific events).

Animal studies tended to confirm a role for cholinergic systems in cognitive processes on the whole, but evidence that cholinergic modulation can exclusively affect memory function has been hard to obtain. Lesions studies using the specific immunotoxin192 IgG-saporin suggest that cholinergic deafferentation of the hippocampus and the neocortex are not sufficient to impair spatial learning (reviewed in McGaughy et al., 2000) although systemic administration of muscarinic antagonists can disrupt place learning in the watermaze in rats (reviewed by McNamara and Skelton, 1993). Global icv infusion of 192 IgG-saporin produces a deficit that can be mimicked by selective cerebellar lesions. This suggests that the impairment is more likely related to the acquisition of the motor skills required to perform a novel spatial task.

Working memory, the capacity to store and manipulate all relevant information required to carry out a single trial, is reliably impaired by both direct and indirect modulation of cholinergic functioning (McGaughy et al., 2000). Working memory is considered a component of executive functioning and is unlikely to be solely dependent on the hippocampus (Rasmussen et al., 1989). Restoration of cholinergic activity may attentuate some of the deficits caused by lesions or receptor blockade in animals (McNamara and Skelton, 1993; McGaughy et al., 2000). Nicotine has also been shown to improve learning and memory on some tasks in animals and the nicotinic antagonist, mecamylamine, can block dentate LTP in vivo (Matsuyama et al., 2000). Attempts have been made to ameliorate some of the cognitive impairments of Alzheimer's disease clinically with drugs that enhance cholinergic function by inhibiting the catabolic enzyme, acetylcholinesterase and also with cholinergic agonists like

nicotine. Although there is evidence of clinical improvement, this is probably more related to attentional rather than mnemonic mechanisms.

3.10 Stress and steroid hormones

Stress-related psychiatric disorders, for example severe depressive disorder and post-traumatic stress disorder, are often associated with cognitive impairment. In patients with depression, these impairments include deficits in delayed match-to-sample (Abas et al., 1990)—a task sensitive to hippocampal dysfunction, explicit (episodic) memory (Bazin et al., 1994) and verbal learning (Shah et al., 1998). Verbal learning impairment in patients with chronic depression correlates with the degree of reduction of hippocampal grey matter apparent with magnetic resonance imaging (Shah et al., 1998). Exposing animals to stress, including the types of stress considered to model aspects of depression in animals by causing learned helplessness, can have a profound effect on hippocampal LTP. The amount of LTP obtained in hippocampal slices taken from rats that had been exposed to inescapable electric shocks profoundly inhibited compared to rats exposed to the same degree of escapable shock (Shors et al., 1989). Many other studies in rodents have replicated the effect on hippocampal synaptic plasticity using different stress regime. Impairments to learning tasks normally dependent on intact hippocampal functioning have sometimes (Shors et al., 1992) but not always (Warren et al., 1991) been found following exposure to "LTP-impairing" stress paradigms.

The effects of stress on both hippocampal learning and function (as measured by LTP) may be mediated via corticosteroid hormones. The hippocampus is rich in receptors for both high affinity Type I (mineralocorticoid) and low affinity Type II (glucocorticoid) receptors. Corticosterone exposure impairs spontaneous alternation behaviour, a behavioural marker of hippocampal damage (Bardgett et al., 1994) and affects acquisition of the radial maze task (Dachir et al., 1993). Removal of the primary source of glucocorticoids by adrenalectomy also impairs spatial learning and memory. There is some evidence that this effect can be reversed by acute corticosterone replacement (McCormick et al., 1997). The selective blockade of central corticosteroid receptors by both MR and GR antagonists delivered icv also disrupts certain components of spatial learning and memory depending on when the injections were made relative to training (Oitzel and de Kloet, 1992).

It is not established if these effects of glucocorticoid modulation are due to alterations to hippocampal LTP? Hippocampal synaptic plasticity can be upregulated or downregulated depending on the levels of stress hormone

(Pavlides et al., 1995). High levels of corticosterone in the rat blocked the induction of LTP and facilitated LTP whereas low levels facilitated LTP. Selective glucocorticoid (Type II) agonists can mimic the effects of high corticosterone levels whereas antagonists at this receptor can prevent stress-induced changes in synaptic plasticity (Xu et al., 1998). Certain neurosteroids may provide protection against the effects of corticosteroids. The effects of corticosterone on rat dentate gyrus LTP in vivo are prevented by co-administration of the neurosteroid dehydroepiandrosterone sulfate (DHEAS) (Kaminska et al., 2000). It should be recognised that long-term exposure to either very low (Sloviter et al., 1989) or very high (Sapolsky et al., 1990) levels of corticosterone will eventually produce morphological changes in the hippocampus.

3.11 Neurotrophic factors

The neurotrophins are a family of at least four structurally related proteins important in neural development and differentiation and also in the survival and unction of neurons in the adult brain. There is evidence of reciprocal regulation since neurotrophin levels are enhanced by neuronal activity (including conditions that induce LTP) and can in turn potentiate synaptic function. Brain derived neurotrophic factor (BDNF) is expressed in the main neuronal types within the CA1 and dentate gyrus cell fields, the pyramidal and the granule cells (Nawa et al., 1997). There is considerable evidence that BDNF can regulate synaptic transmission in the hippocampus both acutely and in the long term. Application of exogenous BDNF to hippocampal slices promotes the induction of LTP by sub-threshold tetanus (Figurov et al., 1996). The use of patch clamp recording techniques suggests that BDNF enhances the neuronal current response to glutamate and that this is due to modulation of the NMDA receptor associated channels (Levine et al., 1998). LTP in CA1 is impaired in mice with a deletion in the coding sequence of the BDNF gene (Korte et al., 1995). The re-expression of this gene in mutant mice using virus-mediated gene transfer restores LTP (Korte et al., 1996).

The influence of BDNF regulation of synaptic function on behaviour has still to be fully determined. Rats treated with antibodies to BDNF (icv) were significantly impaired in a spatial learning task (Mu et al., 1999). Levels of BDNF expression in CA1 were rapidly and selectively increased following contextual fear conditioning, a form of learning also dependent on the hippocampus (Hall et al., 2000).

4. Summary

Conscious recollection describes the access to memories for the facts, events and routes of everyday life. The initial formation, and in some cases retrieval of these memories, probably requires the hippocampus, an area of the brain that receives afferent input from both cortical and subcortical structures. The encoding mechanism for establishing the memory trace must be rapid, potentially long-lasting and capable of acting only on the specific inputs stimulated. The properties of NMDA-dependent long-term potentiation provide a plausible mechanism for this process. Future advances in both the cognitive sciences and neurobiology should lead to the development of sophisticated neural network models that represent the storage and retrieval of information in the complex interconnections of real neuronal populations. There is scope for a myriad of neurochemical factors to influence both LTP induction and maintenance—different neurotransmitters from interconnecting brain areas are likely to regulate, effects of influences, for example, attention, stress, drugs or mood on memory encoding or recall. Although explicit memory function is not the only requirement for conscious awareness, the consequences of severe amnesia for sufferers are profound. Without the ability to learn new associations about their self, the environment and relationships with others, for example, conscious perception cannot advance from the point before the amnesia.

References

Abas, M.A. et al. (1990). *Psychological Medicine* 20, 507–520.
Abraham, W.C. & M.F. Bear (1996). *Trends in Neurosciences* 19, 126–130.
Bannerman, D.M. et al. (1995). *Nature* 378, 182–185.
Bardgett, M.E et al. (1994). *Behavioural and Neural Biology* 61, 186–190.
Barnes, C.A. & B.L. McNaughton (1985). *Neuroscience* 99, 1040–1048.
Bazin, N. et al (1994). *Psychological Medicine* 24, 239–245.
Beck, H. (2000). *Journal of Neuroscience* 20, 7080–7086.
Bittar, P. & D. Muller (1993). *Brain Research* 620, 181–188.
Bliss, T.V.P. & G.L. Collingridge (1993). *Nature* 361, 31–39.
Bliss, T.V.P. & T. Lomo (1973). *Journal of Physiology* 232, 331–356.
Bliss, T.V.P. & G. Richter-Levin (1993). *Hippocampus* t3, 123–126.
Bortolotto, Z.A. et al. (1994). *Nature* 368, 740–743.
Brucato, F.H. et al. (1996). *Neuroscience* 74, 331–339.
Brun, V.H. et al. (2001). *Journal of Neuroscience* 21, 356–362.
Castro, C.A. et al. (1989). *Nature* 342, 545–548.

Christie, B.R. & W.C. Abraham (1992). *Neuron* 9, 79–84.

Chun, M.M. & E.A. Phelps (1999). *Nature Neuroscience* 2, 844–847.

Clugnet, M.-C. & J.E. LeDoux (1990). *Journal of Neuroscience* 10, 2818–2824.

Colley, P.A. et al. (1990). *Journal of Neuroscience* 10 3353–3360.

Collingridge, G.L. et al. (1983). *Journal of Physiology* 334, 33–46.

Dachir, S. et al. (1993). *Behavioural and Neural Biology* 60, 103–109.

Danysz, W. et al. (1995). *Behavioural Pharmacology* 6, 455–474.

Davies, C.H. et al. (1991). *Nature* 349, 609–611.

Eichenbaum, H. (1999). *Nature Neuroscience* 2, 775–776.

Figurov, A. et al. (1996). *Nature* 381, 706–709.

Fujii, S. et al. (1991). *Brain Research* 555, 112–122.

Grunwald, T. (1999). *Proceeding of the National Academy of Sciences (USA)* 96, 12083–12089.

Hall, J. et al. (2000). *Nature Neuroscience* 3, 533–535.

Hebb, Donald O. (1949). *The Organisation of Behaviour.* (p. 62) New York: John Wiley & Sons.

Helmstaedter, C. et al. (1997). *Brain and Cognition* 35, 110–131.

Hesse & Teyler (1976). *Nature* 264, 562–564.

Huang, Y.-Y. et al. (1992). *Science* 255, 730–733.

Izquierdo, I. & J.H. Medina (1995). *Neurobiology of learning and memory* 63, 19–32.

James, W. (1890). *The Principles of Psychology,* New York: Macmillan Publishing Co Inc.

Jeffery, K.J. & I.C. Reid (1997). *American Journal of Psychiatry* 154, 156–164.

Kaminska, M. et al. (2000). *Brain Research Bulletin* 52, 229–234.

Keith, J.R. & J.W Rudy (1990). *Psychobiology* 18, 251–257.

Kim, J.J. & K.S. Yoon (1998). *Trends in Neurosciences* 21, 505–509.

Korte, M. et al. (1995). *Proceeding of the National Academy of Sciences (USA)* 92, 8856–8860.

Korte, M. et al. (1996). *Proceeding of the National Academy of Sciences (USA)* 93, 12547–12552.

Laroche, S. (1990). *Neuroscience Letters* 114, 184–190.

Levine, E.S. et al. (1998). *Proceedings of the National Academy of Sciences (USA)* 95, 10235–10239.

Lynch, G. et al. (1983). *Nature* 305, 719–721.

Maren S. & M. Baudry (1995). *Neurobiology of Learning and Memory* 63, 1–18.

Martin, S.J. et al. (2000). *Annual Reviews in Neuroscience* 23, 649–711.

Matsuyama, S. et al. (2000). *European Journal of Neurosciences* 12, 3741–3747.

McCormick, C.M. et al. (1997). *Behavioral Neuroscience* 111, 518–531.

McGaugh, J.L. (1966). *Science* 153, 1351–1358.

McGaughy, J. et al. (2000). *Behavioural Brain Research* 115, 251–263.

McNamara, R.K. & R.W. Skelton (1993). *Brain Research Reviews* 18, 33–49.

McNaughton, B.L. et al. (1986). *Journal of Neuroscience* 6, 563–571

Mott, D.D. et al. (1990). *Neuroscience Letters* 113, 222–226.

Moser, E.I. et al. (1998). *Science* 281, 2038–2042

Morris, R.G.M. et al. (1986). *Nature* 319, 774–776.

Morris, R.G.M. et al. (1982). *Nature* 297, 681–683.

Mu, J.-S. et al. (1999). *Brain Research* 835, 259–265.

Nawa, H. et al. (1997). *Critical Reviews in Neurobiology* 11, 91–100.

Oitzl, M.S. & E. R. de Kloet (1992). *Behavioural Neuroscience* 106, 62–71.

Pavlides, C. et al. (1995). *Neuroscience* 68, 387–394.

Rasmussen, M. et al. (1989). *Psychobiology* 17, 335–348.

Reid, I.C. & C.A. Stewart (1997). *Seizure* 6, 351–359.

Reidel, G. et al. (1999). *Nature Neuroscience* 2, 898–905.

Sanes, J.R. & J.W. Lichtman (1999). *Nature Neuroscience* 2, 597–604.

Sapolsky, R.M. et al. (1990). *Journal of Neuroscience* 10, 2897–2902.

Sara, S.J. (2000). *Learning and Memory* 7, 73–84.

Seabrook, G.R. et al. (1997). *Neuropharmacology* 36, 823–830.

Shah, P.J. et al. (1998). *British Journal of Psychiatry* 172, 527–532.

Shors, T.J. & E. Dryver (1992). *Psychobiology* 20, 247–253.

Shors, T.J. et al. (1989). *Science* 244, 224–226.

Silva, A.J. et al. (1992a). *Science* 257, 201–206.

Silva, A.J. et al. (1992b). *Science* 257, 206–211.

Sloviter, R.S. et al. (1989). *Science* 243, 535–538.

Squire, Larry R. (1986). *Science* 232, 1612–1619.

Staubli, U. & J. Scafidi (1997). *Journal of Neuroscience* 17, 4820–4828.

Warren, D.A. et al. (1991). *Psychobiology* 19, 127–134.

Willshaw, D. & P. Dayan (1990). *Neural Communications* 2, 85–93.

Wilsch, V.W. et al. (1998). *Journal of Neuroscience* 18, 6071–6080.

Wilson, M.A. & S. Tonegawa (1997). *Trends in Neurosciences* 20, 102–106.

Xu, L. et al. (1998). *Proceeding of the National Academy of Sciences (USA)* 95, 3204–3208.

Young, G.B. & Pigott S.E. (1999). *Archives of Neurology* 56, 153–157.

Zola-Morgan, S. et al. (1986). *Journal of Neuroscience* 6, 2950–2967.

Motivation

Reward and punishment systems

Heather Ashton

1. Introduction

Human behaviour is powerfully influenced by a delicate, and sometimes uneasy, balance of activity between brain reward and punishment systems. In general, activities that are pleasurable or rewarding are pursued while those that are aversive or punishing are avoided. The control of such behaviour implies the existence of a mechanism for selecting appropriate goals, for initiating the behaviours required to achieve them, and for signalling when they have been achieved. If a goal proves favourable, it is advantageous to reinforce the behaviour leading to it; if the goal proves unfavourable, the behaviour leading to it must be suppressed and avoidance action taken in future. Such a signalling system appears to be provided by central 'reward' and 'punishment' pathways in the brain. These pathways are closely integrated with systems for arousal and for learning and memory and are fundamental for motivation, goal-seeking and avoidance behaviour. They are thought to form the basis for drives such as hunger, thirst and sex, and to contribute to complex emotional/cognitive states such as hope and disappointment.

In humans, at least, reward and punishment systems are clearly involved in conscious thought and behaviour. For example, anticipated rewards may be consciously deferred and relatively aversive activities carried out with the prospect of a future pleasurable goal. Conversely, instant pleasure may sometimes be seized despite knowledge of future punishment. Clearly, a degree of consciousness is required to choose the options. Almost every conscious activity carries some affective tone (Edelman & Tononi, 2000; Greenfield, 2000); without this, there would be no motivation to do anything at all. This situation is seen in the anhedonia and apathy which sometimes accompanies schizophre-

nia, depression, some dementias and Parkinson's disease (Chapters 14–18). These negative symptoms "reflect fundamental impairments in basic brain mechanisms that underlie goal-directed behaviour" (Brown & Pluck, 2000).

2.   Pathways of reward

2.1   Intracranial self-stimulation (ICSS)

The idea of reward and punishment systems in the brain stemmed from the serendipitous discovery by Olds and Milner (1954) that rats would work to obtain electrical stimulation through electrodes implanted at specific sites in the brain. When allowed to stimulate themselves by pressing a lever, they would sometimes do so at rates of over 100 times a minute for hours at a time. It appeared that such stimulation was rewarding; the rats seemed to 'like' the sensation so much that the brain sites supporting ICSS came to be known as "pleasure centres." Furthermore, motivation for self-stimulation was so strong that when food reward and the opportunity for ICSS, especially from the lateral hypothalamus (an area related to feeding mechanisms), were both restricted, the animals preferred the stimulation, even at the cost of starvation (Routtenberg, 1978). At other sites, ICSS was only obtained if the rats were motivated by thirst or sexual arousal rather than hunger (Redgrave & Dean, 1981; Routtenberg, 1978). Such findings suggested that the effects of ICSS and natural reward were similar and that rewarding stimulation sites were located in neural pathways which physiologically subserve reinforcement of goal-directed behaviour.

Sites which support ICSS have been found in all vertebrate species studied, including man, and patients with implanted electrodes describe different sensations of pleasure depending on the electrode locations (Heath, 1964; Redgrave & Dean, 1981). As shown in Table 1, a large number of brain sites support ICSS (Redgrave & Dean, 1981; Routtenberg, 1978). These sites are widely distributed in the brain from the frontal lobes to the medulla, and include areas of very different function, from sensory processing to motor activity. Self-stimulation is also supported from sites in the fibre tracts connecting many of these areas, notably the median forebrain bundle. Most, if not all, sites which support ICSS have anatomical connections with limbic structures, where the emotional, autonomic and motor responses appropriate to reward may be generated. Many of these same pathways are also involved in arousal and in learning and memory systems. The discovery of brain rewarding areas seems to hold

Table 1. Some sites which support intracranial self-stimulation (ICSS) in various animal species

Brain area	Sites which support ICSS	
Forebrain	frontal cortex	entorhinal cortex
	olfactory nucleus	caudate nucleus
	nucleus accumbens	entopeduncular nucleus
	septal area	hippocampus
	amygdala	ventral and medial thalamus
	hypothalamus	median forebrain bundle
		dorsal noradrenergic bundle
Midbrain and brainstem	ventral tegmental area	substantia nigra
	raphe nuclei	nucleus coeruleus
	superior cerebellar peduncle	periaqueductal grey
	mesencephalic nucleus of trigeminal nerve	
Cerebellum	deep cerebellar nuclei other cerebellar areas	
Medulla	motor nucleus of trigeminal nerve	
	nucleus of tractus solitarius	

References: Redgrave & Dean 1981; Routtenberg, 1978

the key for understanding the normal processes of motivation, reinforcement and learned behaviour.

3. The neurochemistry of reward

3.1 Dopamine

There is strong evidence that dopamine is an important neurotransmitter in reward pathways. Dopaminergic pathways in the median forebrain bundle include the nigrostriatal pathway from substantia nigra to caudate nucleus and the mesolimbic pathway from the ventral tegmental area to the nucleus accumbens, olfactory tubercle, septal area and frontal cortex (Chapter 1). Neuronal mapping and stimulation studies of ventral tegmental areas indicate that ICSS is closely associated with dopamine containing cells (Wise & Bozarth, 1987). Drugs which disrupt dopamine synthesis or block dopamine receptors disrupt ICSS from a number of sites. When dopamine blockade is limited to one hemisphere, self-stimulation responses are suppressed for that hemisphere but not

for the other. Drugs which increase dopaminergic activity (amphetamine, cocaine) increase rates of ICSS, are avidly self-administered by animals, and are drugs of abuse in man (see below). In humans the hedonic response to amphetamine correlates positively with the magnitude of dopamine release in the ventral tegmentum (Drevets et al., 2001).

In a fascinating series of experiments, Stein and Belluzi (1988, 1989) demonstrated that the firing rate of individual neurons in the hippocampal CA_1 area (another site supporting ICSS) in isolated rat brain slices could be modified by microinjection of dopamine or cocaine. The preparation was arranged so that increased neuronal firing rates could trigger a self-microinjection of dopamine or cocaine into individual neurons. When delivered randomly the drugs had little effect on the firing rate of the cells, but after suitable priming, cells responded by increasing their firing rates contingently to trigger microinjections of cocaine or dopamine, but not placebo or opioid injections. Thus the activity of individual, isolated, cells could apparently be reinforced by dopaminergic drugs. It seemed that, even at the cellular level, animals are programmed to seek reward. In parallel experiments in intact rats, dopamine and cocaine reinforced self-administration when injected into the same CA_1 hippocampal field but not into other hippocampal areas. Other hippocampal cells responded specifically to opioids but not to dopamine.

These results led to the suggestion that the functional unit of reward is a population of individual neurons ('hedonistic neurons') scattered around reward areas of the brain which are specifically responsive to certain transmitters and are presumably connected to pathways controlling motivated behaviour. Phillips and Fibiger (1989) demonstrated an increase in dopamine metabolism, synthesis and release in the ventral tegmental area and nucleus accumbens during ICSS in rats, an increase proportional to the stimulation rate and intensity.

Much of the early work implicating dopamine in reward systems has been vindicated, but also extended and refined. For example, recent evidence suggests that dopamine acts not simply as a reinforcer of rewarding actions, but is involved in the formation of contextual stimuli, whether rewarding or aversive (Spanagal & Weiss, 1999; Schultz et al., 1997; Wickelgren, 1997; Ikemoto & Panksepp, 1999). Le Moal and Simon (1991) and Koob (1992) argue that the dopaminergic mesocorticolimbic system acts as a modulator or filtering mechanism for signals from the limbic system mediating basic biological drives and motivational variables. These signals are then translated into motor behaviour via the extrapyramidal motor system. These authors emphasise that dopaminergic systems are involved in many other activities apart from reward, includ-

ing cognitive functions such as learning and memory and general regulation of adaptive behaviour. In line with this view, Di Chiara (1995) posits a dual role for dopamine in motivation: the learning of incentive properties of various stimuli and the transduction of salient stimuli into goal-directed responses.

3.2 Noradrenaline

Some brain sites which support ICSS are not near a dopaminergic system, and many sites which elicit self-stimulation coincide with histological maps of noradrenergic nerve distribution (Stein, 1978; Fig. 3, Chapter 1). In particular, a dorsal noradrenergic pathway originates in the locus coeruleus and innervates the neocortex, cerebellum, hippocampus and thalamus. A ventral pathway originates from noradrenaline-containing cells in the medulla and pons and innervates the hypothalamus and ventral parts of the limbic system. All these pathways, and the locus coeruleus itself, support ICSS and stimulation of rewarding areas in the median forebrain bundle is accompanied by increased release of noradrenaline and its metabolites from the lateral hypothalamus, while stimulation of neutral sites does not (Stein & Wise, 1969). Depletion of noradrenaline, inhibition of synthesis, or blockade of alpha-adrenergic receptors suppresses ICSS. However, it appears that neuroadrenergic activity in ICSS operates through a dopaminergic link, since complete disruption of the locus coeruleus has little effect on the rate of self-stimulation from an electrode in the dorsal midbrain of rats (Routtenberg, 1978), and drugs which disrupt dopamine synthesis or block dopamine receptors disrupt ICSS from the locus coeruleus. While certain levels of noradrenergic activity appear to be rewarding, excessive activity is aversive and is probably involved in the generation of fear and anxiety (Charney et al., 1995; Redmond, 1987) and in some drug withdrawal states (Nutt, 1996).

3.3 Endogenous opioids

Opioid systems interact closely with dopaminergic and noradrenergic systems in reward pathways. In many brain areas the distribution of cell bodies containing endogenous opioids and of opioid binding sites overlaps with that of catecholamine-containing cell areas, and reinforcing sites for ICSS (including amygdala, locus coeruleus, pontine central grey, zona compacta of substantia nigra, bed nucleus of stria terminalis and nucleus accumbens) contain beta-endorphin and other polypeptides as well as catecholamines with which they may be co-released (Elde et al., 1976). Furthermore, the increase in self-

stimulation behaviour induced by dopaminergic drugs is blocked by naloxone (Schaefer & Michael, 1990), suggesting an opioid link. Conversely, rats will work to self-inject morphine specifically into the ventral tegmental area, but this behaviour is partially suppressed by the dopamine receptor antagonists or by lesions of ascending dopaminergic pathways (Cooper, 1984). The role of opioids in reward is also indicated by the findings, referred to above (Stein & Belluzi, 1988, 1989), that isolated cells in brain slices of CA_3 hippocampal fields would increase their firing rate to trigger a microinjection of the endogenous opioid dynorphin A but did not respond to dopamine, while dynorphin A, but not dopamine or cocaine, reinforced self-administration into the CA_3 hippocampal area in intact rats.

Opioids have been shown to increase the release of dopamine in the nucleus accumbens but they also subserve reinforcement in animals by a non-dopaminergic mechanism (Di Chiara & North,1992; Koob, 1992). Physiologically the opioid system appears to be largely involved in the consumatory rewards of feeding, drinking, sexual and maternal behaviour (Koob, 1992; Di Chiara & North, 1992) and certain types of social behaviour (Panksepp, 1981; Bolles & Fanselow, 1982).

3.4 Glucocorticoids

Substantial evidence, reviewed by Piazza and Le Moal (1998), indicates that glucocorticoids are involved in reward systems. In the rat, corticosterone, the main glucocorticoid in this species, appears to have intrinsic rewarding effects. Rats will intravenously self-administer corticosterone which exhibits a dose-response curve similar to that of other reinforcing drugs. The rate of self-administration can be altered by changing the strength of infusion suggesting that the animals attempt to maintain an optimal level of reinforcement. Corticosterone also enhances the positive reinforcing actions of cocaine, amphetamine, opioids and alcohol, an effect that is reversed by adrenalectomy or inhibition of corticosterone synthesis. Glucocorticoid secretion is well known to be increased by stress, which has also been shown to increase the self-administration of a range of rewarding drugs. Piazza and Le Moal (1998) suggest that the positive reinforcing actions of glucocorticoids constitute a protective response which reduces the aversive effects of stress, enabling the individual to cope with it better. These effects may be mediated by an interaction with dopamine; glucocorticoids enhance activity in dopaminergic mesencephalic pathways, increasing both dopamine release and the sensitivity of postsynaptic dopamine receptors. In humans, as well as in animals, in-

teractions between individual reactions to stress, glucocorticoid secretion and dopaminergic activity have implications for vulnerability to drug dependence as discussed further below.

3.5 Gaba-aminobutyric acid (GABA)

Another aspect of reward is relief from aversive stimuli (negative reward). This aspect appears to be largely supplied by GABA, the most widely distributed inhibitory transmitter in the brain. GABA receptors are found in many areas associated with reward such as amygdala, nucleus accumbens, substantia nigra, periaqueductal grey, frontal cortex and cerebellum (Koob, 1992). Drugs which potentiate GABA activity (benzodiazepines, barbiturates, alcohol) have characteristic actions which include euphoria, disinhibition and anxiety reduction, as well as sedation and hypnosis. These actions correlate well with the ability of these drugs to increase chloride conductance through $GABA_A$ receptors, resulting in post-synaptic inhibition due to hyperpolarisation (Koob, 1992). All of these drugs cause a release of punished responding in animals, which is blocked by $GABA_A$ receptor antagonists, and which also correlates with the drugs' anxiolytic activity in humans (Sepinwall & Cook, 1979). This anxiolytic property may be a major component of the reinforcing actions of these drugs and Koob (1992) suggests that it is exerted through GABA activity in limbic and extrapyramidal regions. An important site may be the efferent connections from the nucleus accumbens to the substantia inomminata-ventral pallidium which are thought to be GABA-ergic (Koob, 1992).

Benzodiazepines and barbiturates are self-administered by animals (Koob, 1992). Unlike other rewarding drugs, these are not believed to release dopamine from the nucleus accumbens or prefrontal cortex (Nutt, 1996; Di Chiara & Imperato, 1988; Spanagel & Weiss, 1999). However, it is possible that they do so when used for euphoric effects in the high dosages used by benzodiazepine abusers (Strang et al., 1993).

3.6 Other neurotransmitters

Many other neurotransmitters are undoubtedly involved in reward systems (Nutt, 1996). These include cholecystokinin, glutamate, neuropeptide Y, anandamides and others, each of which have many other actions and also act on multiple receptor subtypes. These substances not only interact with other reward neurotransmitters but also take part in a delicate balance of activity with reciprocally connected punishment systems.

4.   Pathways of punishment

Activity at certain brain sites appears to generate sensations that are strongly aversive. Animals will work as energetically to avoid electrical stimulation at such sites as they will to obtain stimulation at rewarding points (Olds & Olds, 1963). A major anatomical pathway subserving aversive effects appears to be the periventricular system, a group of fibres running between midbrain and thalamus with branches to hypothalamus, limbic nuclei (including amygdala and nucleus accumbens), cerebral cortex and hippocampus (Stein, 1968). This system probably interacts with the median forebrain bundle, since both pathways distribute fibres to common sites (Levitt & Lonowski, 1975). A second pathway subserving aversion may originate in the dorsal raphe nuclei (Fig. 5, Chapter 1), distributing to periventricular regions but including some fibres which run in the median forebrain and terminate in various parts of the limbic system (Stein & Wise, 1974). Destruction of either of these pathways results in a generalised defect of passive avoidance, so that an animal will no longer suppress behaviour that precipitates an aversive stimulus such as an electric footshock. Thirdly, noradrenergic projections from the locus coeruleus (Fig. 4, Chapter 1) appear to be involved in fear and flight reactions. The locus coeruleus has efferent and afferent connections with cortex, hippocampus, amygdala and other brain areas and also receives afferents from the raphe nuclei and several sensory relay areas (Charney et al., 1995). Fourthly, a large component of aversive mechanisms must be provided by the systems responsible for signalling pain and nociception, including the central projections of the spinothalamic and spinoreticular tracts to brainstem, limbic system, thalamus and sensory cortex (Thompson, 1984).

These interconnected pathways may act as a 'punishment' system favouring avoidance behaviour and also encouraging selection of the appropriate reward behaviour that will terminate a particular aversive state, such as feeding in hunger, drinking in thirst (Stein, 1971) or flight in fear (Charney et al., 1995). The interaction between reward and punishment systems allows for many dimensions of reward and punishment. Activity in reward systems not only engenders positive reward, but also inhibits activity in punishment systems; conversely activity in punishment systems is not only aversive but also inhibits activity in reward systems. There could be innumerable degrees of partial inhibition or excitation in the different pathways, resulting in finely graded nuances of reward/punishment activity. In addition, both reward and punishment systems are closely integrated with those for learning and memory. Thus, lack of expected reward, as well as active punishment, is unpleasant

Table 2. Some emotions that accompany activity in reward and punishment systems

	Emotions	Putative neurotransmitters (much simplified)
REWARDS		
Positive reinforcement	pleasure, joy, ecstasy	dopamine noradrenaline serotonin corticosteroids
Consummation of reward fulfilment of goal	repletion, contentment triumph	opioids GABA
Anticipation of reward	hope	acetyl choline dopamine
Negative reinforcement alleviation of punishment omission of expected punishment	relief	GABA acetyl choline opioids
PUNISHMENTS		
Positive aversion	hunger, thirst pain, fear/panic craving	acetylcholine serotonin noradrenaline substance P glutamate
Anticipation of punishment	anxiety	acetyl choline serotonin noradrenaline
Omission of expected reward failure to achieve goal	disappointment despondence	acetyl choline serotonin dopamine

(disappointment); lack of expected punishment, as well as active pleasure, is rewarding (relief) (Table 2). The hippocampal comparator system (Gray, 1982) is thought to be involved in forming the expectation of reward or punishment as a result of learning. Many of these expectations of hope or fear clearly reach consciousness.

5.   The neurochemistry of punishment

5.1 Acetylcholine

The periventricular system appears to be at least partly cholinergic (Stein, 1968). A deficit of passive avoidance of aversive stimuli is produced by surgical destruction of this pathway. Local application of anticholinergic drugs produces similar effects which are reversed by local instillation of cholinergic drugs. Cholinergic systems are also closely involved with learning and memory (Chapter 4) and it is likely that some functions requiring suppression of learned behaviour are mediated through the periventricular system. As mentioned above, the periventricular system communicates with the limbic circuit, and many limbic structures receive innervation from both the periventricular system and the median forebrain bundle. The two acting together can thus be envisaged to promote the seeking of reward and the suppression of punished behaviour.

5.2 Noradrenaline

The source of over 70% of noradrenaline in the brain is the locus coeruleus and many studies reviewed by Redmond (1987), Charney et al. (1995) and Valentino and Aston-Jones (1995) indicate that this nucleus, with its associated adrenergic projections, is a neural substrate for normal and pathological anxiety and for panic and post-traumatic stress disorder, aversive conditions which certainly reach consciousness. Electrical stimulation of the locus coeruleus in primates elicits fear and anxiety reactions while lesions of the nucleus reduce fear responses. Agents which increase locus coeruleus activity (alpha 2 adrenergic receptor antagonists) induce anxiety in normal humans and panic in susceptible patients, while drugs which reducing the firing rate of the locus coeruleus (alpha 2 adrenergic receptor antagonists, benzodiazepines) prevent these effects and also have clinical anxiolytic activity. A variety of stressful and aversive stimuli, including pain and somatic discomfort, increase noradrenaline turnover in the locus coeruleus, limbic regions and cerebral cortex. Charney et al. (1995) point out that noradrenergic output from the locus coeruleus is highly regulated by other neurotransmitters including opioids, GABA, serotonin, acetylcholine, and corticotrophin releasing factor (CRF). Although it is not possible to separate out the effects of a single neurotransmitter, these authors suggest that the locus coeruleus is a key component in the efferent arm of the neural circuit of anxiety. This noradrenergic system may be impor-

tant in the planning and execution of behaviours (such as escape), appropriate for survival under different forms of threat.

5.3 Serotonin (5-HT)

Serotonin appears to play a dual role in reward and punishment (Tyers & Hayes, 1992). Both the ventral tegmental area and the nucleus accumbens receive serotonergic projections from dorsal and median raphe nuclei. Serotonergic activity in the ventral tegmentum is excitatory, resulting in increased dopamine release in the nucleus accumbens. However, serotonergic neurons from the raphe nuclei inhibit dopaminergic neurons in the nucleus accumbens itself. Thus serotonergic pathways to the dopaminergic mesolimbic system exert opposing effects, exciting activity in the ventral tegmentum but inhibiting that in the nucleus accumbens. It is not clear whether the outputs from the dorsal and median raphe nuclei subserve different functions in the reward-punishment spectrum or whether the opposing effects are mediated by different serotonergic receptors.

Activity in the raphe nuclei depends to a large extent on an excitatory noradrenergic input from the locus coeruleus and there is considerable evidence indicating that serotonin, like noradrenaline, is involved in fear and anxiety. In both animals and humans, agonists of 5-HT_{1A} receptors (which inhibit serotonin release) have anxiolytic effects. The hippocampus, a limbic structure strongly implicated in anxiety (Gray, 1982), also contains 5-HT_{1A} receptors and agonists of these receptors cause a dose-dependent decrease in the amplitude of firing of cells. Dourish et al. (1986) suggest that the anxiolytic effects of 5-HT_{1A} receptor agonists result from inhibition of neural firing in the raphe nuclei and decreased serotonin synthesis both locally and in terminal regions including cortex, amygdala and septo-hippocampal projections. Agonists of 5-HT_2 receptors, which increase serotonergic activity, are anxiogenic and can provoke panic attacks, while 5-HT_2 receptor antagonists have anxiolytic actions.

Other anxiolytic drugs affect serotonergic activity indirectly. For example, benzodiazepines decrease both noradrenaline and serotonin release and turnover and decrease the firing rate of both locus coeruleus and raphe nucelei, and much of the anxiolytic effect of benzodiazepines may be mediated through inhibition of serotonergic activity (Gray, 1982). Thus both serotonergic and noradrenergic systems appear to be crucially involved in the generation of anxiety. The complex interactions between stress, serotonin and corticosteroids are reviewed by Chaouloff (2000).

The dual action of serotonin in reward-punishment is further complicated by the findings that *low* central serotonergic activity is associated with other aversive states such as depression, drug dependence (especially craving), bulimia and aggressive disorders. These states are often accompanied by anxiety and can be alleviated by drugs which increase serotonergic activity, i.e. antidepressants, especially specific serotonin reuptake inhibitors (SSRIs). Deakin et al. (1992) suggest that the dorsal and median raphe nuclei mediate two different systems affecting different 5-HT receptors. On this hypothesis, pathways from the dorsal raphe nucleus to frontal cortex and amygdala are activated by acute aversive stimuli or threats and lead to fear/anxiety and escape/avoidance behaviour by stimulation of 5-HT_2 receptors. Repeated or chronic aversive stimuli, however, lead to a degree of tolerance described as stoicism or resilience. This response is mediated through pathways from the median raphe nuclei to the hippocampus, activating 5-HT_{1A} receptors which inhibit excessive release of serotonin. Breakdown of this coping system may result in depression which is seen as an impairment of 5-HT_{1A} function.

5.4 Pain neurotransmitters: Substance P, glutamate

Pain and fear of pain are perhaps the most powerful of aversive stimuli and the most immediately important for survival since they carry the threat of tissue damage. Melzack and Wall (1988) described three components of pain: sensory-discriminative from peripheral nociceptors, emotional or motivational-affective, involving limbic system punishment pathways, and rational or cognitive-evaluative derived from cerebral cortex. Excitatory and inhibitory feed-back systems link all components.

Afferent fibres from peripheral nociceptors enter the dorsal horn and substantia gelatinosa of the spinal cord. Here the main excitatory neurotransmitter appears to be substance P, an undecapeptide which is released in a dose-dependent manner specifically in response to stimulation of nociceptive neurons and excites only those neurons which respond to noxious stimuli. Substance P produces slow excitatory presynaptic potentials in dorsal horn neurons and it may be co-released with a fast-acting neurotransmitter such as glutamate. Glutamate may be involved in plastic changes following repetitive nociceptor stimulation (Dickenson, 1990). In particular, activation of NMDA receptors produces a long-lasting increase in the firing rate of dorsal horn cells, amplifying, enhancing and prolonging the initial nociceptive discharge. This phenomenon is akin to hippocampal long-term potentiation (Chapter 4) and may be important in prolonged nociceptive hypersensitivity states and chronic

pain syndromes (Dubner & Ruda, 1992). Other excitatory peptides involved in central nociception pathways are described by Yaksh and Aimone (1989). The pharmacology of the supraspinal projections reaching mesencephalic and diencephalic sites is poorly understood, but the main excitatory neurotransmitter appears again to be glutamate.

5.5 Pain modulators: Monoamines, acetyl choline, GABA, endogenous opioids

Acute pain and fear of pain clearly subserve a useful function in protecting the body from injury, both by evoking an immediate withdrawal reaction and by providing an aversive stimulus which, through learning and memory, promotes future avoidance of noxious stimuli. The somatic reaction to acute and expected pain is one of general arousal with cortical, autonomic, motor and endocrine activation well adapted for fight or flight behaviour (Deakin et al., 1992). However, if circumstances demand sustained physical activity, it may also be adaptive to inhibit pain sensation. Subserving this function, powerful pain suppressive systems are temporarily activated by stress. These include descending pathways to the spinal cord dorsal horn neurons from periaqueductal grey and medullary raphe nuclei and from the lateral reticular formation in addition to gate-control mechanisms within the spinal cord (Melzack & Wall, 1988).

Several neurotransmitters and modulators are involved in pain suppressant pathways. Descending impulses from the periaqueductal grey medullary raphe nuclei release serotonin while those from the lateral reticular formation release noradrenaline (Yaksh and Aimone, 1989). The therapeutic effects of antidepressants in chronic pain are thought to be at least partly due to facilitation of these systems. Another pain inhibitory pathway from the substantia nigra may be dopaminergic. Fitzgerald (1986), and Hartvig et al. (1989) review evidence that acetylcholine, acting on muscarinic receptors in the spinal cord, has antinociceptive activity. In addition, GABA modulates glutamate activity in the spinal cord and brain (Yaksh & Aimone, 1989). Recently it has become apparent that endogenous cannabinoid systems are also involved in central, and probably peripheral, pain modulation (Piomelli et al., 2000).

The most potent and pervasive pain suppression system appears to be provided by endogenous opioids, particularly methionine encephalin and beta endorphin. These opioids and their receptors are widely distributed at several levels in the central nervous system (Mansour et al., 1988). Enkephalins appear to control the responses of dorsal horn neurons and may also modulate pain

at supraspinal sites. Enkephalinergic systems in the spinal cord and elsewhere are probably tonically active in pain modulation, but the beta-endorphin system and further enkephalinergic activity are triggered into action by noxious stimuli and a large variety of stresses (Bolles & Fanselow, 1982). In these conditions beta-endorphin may be co-released with ACTH from the pituitary gland, enkephalins with adrenaline from the adrenal medulla, and noradrenaline from peripheral nerves as part of the general reaction to stress (Hughes, 1983). High concentrations of opioid receptors are found throughout the limbic system, especially in the amygdala, and opioid systems are believed to be important in modulating the affective and cognitive components of pain. A specific role for the amygdaloid opioid system in generating an emotional component to painful experiences has been postulated by several authors (Kapp & Gallagher, 1979; Mishkin & Appenzeller, 1987). It is suggested that the amygdala encodes, stores and retrieves the hedonic qualities, rewarding or aversive, of all sensory stimuli. In this function it interacts with the hippocampus which at the same time encodes the environmental context of each specific memory.

Opioid systems are intimately involved in "the whole pleasure-pain modality" (Bolles & Fanselow, 1982) and affect conscious and unconscious behaviour. Though acutely painful stimuli may press urgently into consciousness, inhibitory modulators serve to remove pain from the conscious level allowing appropriate adaptive behaviour. Thus a soldier wounded in battle may feel no pain until removed from the front and potentially painful stimuli may pass unnoticed during the excitement of sporting activities (Melzack & Wall, 1988).

6.   Individual susceptibility to reward and punishment

Susceptibility to reward and punishment varies between individuals as a result of genetic and to some extent environmental factors (Altman et al., 1996). These factors may also contribute to personality types and temperaments (Cloninger, 1994). Thus individuals with high sensitivity to punishment tend to have anxiety-prone personalities. In the field of drug dependence, such subjects tend to prefer anti-anxiety (de-punishing) drugs and to avoid stimulants. Conversely, those who are high in novelty seeking, relatively antisocial, and low in harm avoidance are postulated to have low sensitivity to punishment. They may also have low sensitivity to reward, requiring extra, often risk-taking, stimulation to feel rewarded. In the field of drugs, they prefer psychostimulants. Between these extremes, any combination of low or high sensitivity of reward and punishment systems is theoretically possible. The particular combination

of reward/punishment sensitivity that a person inherits or develops may be of importance in determining his/her general behaviour as well as vulnerability to drug addiction, anxiety disorders, depression and chronic pain syndromes which are discussed below.

7. Dysfunction of reward and punishment systems: Effects on motivation

Dysfunction of reward and punishment systems can distort motivation in a number of ways. A few examples are briefly outlined here to illustrate how this finely tuned survival mechanism can be perverted by false rewards and pathological punishments.

7.1 Drug addiction

Drug addiction has been described as "a cycle of spiralling dysregulation of brain reward systems that progressively increases, resulting in compulsive drug use and a loss of control over drug-taking" (Koob & Le Moal, 1997). The motivational disturbance can be such that all other goals are virtually subsumed by drug-seeking behaviour. The drug abuser may be driven to take the drug "even though he/she does not consciously want to do so" (Volkow et al., 1999). Addictive behaviour in humans bears an uncanny resemblance to reward-seeking ICSS and compulsive drug self-administration in animals. For example, under certain conditions monkeys will spontaneously self-administer amphetamine-like drugs in increasing doses up to the point of death, forsaking all other drives (Villareal & Salazar, 1981).

Nearly all addictive drugs (cocaine, amphetamine, nicotine, alcohol, opiates, cannabis, ecstasy and others) induce dopamine release in the nucleus accumbens, prefrontal cortex or both (Nutt, 1996) and it has been argued that dopaminergic activation in these rewarding areas is the final common pathway for all addictive drugs (Di Chiara & Imperato, 1988; Wise & Bozarth, 1987). Other reward transmitters (opioids, GABA, monoamines) and brain regions (globus pallidus, amygdala, locus coeruleus and raphe) are almost certainly also involved (Koob, 1992; Nutt, 1996; Self, 1998), some through a dopaminergic link.

Although initially many addictive drugs produce "pure" pleasure, continued use can lead to sensitisation or tolerance due to homeostatic changes in reward systems (Spanagel & Weiss, 1993; Self, 1998). As these processes con-

tinue, lack of sufficient drug produces withdrawal effects. Such effects are often dominated by a subjective craving. This feeling, possibly due to relative over-activity of punishment systems, and decreased dopamine release from reward systems (Spanagel & Weiss, 1999), also leads to drug-seeking behaviour. At this stage, however, the initial motivation for reward is displaced to a varying extent by the motivation to avoid or alleviate the punishment of withdrawal.

Tolerance, sensitisation, craving, withdrawal and relapse may actually be more complicated than indicated above and may involve separate mechanisms which are too complex to summarise here (See Altman et al., 1996). Recent research on specific drugs of abuse is reviewed by several authors in a special issue of *Trends in Pharmacological Sciences* 13: 169–219 (1992). However, the concept of addiction as "an emotional fixation ... acquired through learning, which intermittently or continually expresses itself in a purposeful stereotyped behaviour with the character and force of a natural drive, aiming at a specific pleasure or the avoidance of specific discomfort" (Bejerot, 1980) still broadly applies.

Vulnerability to drug abuse has been associated with low serotonergic activity and with stress. There is evidence (reviewed by Ashton and Young, 1999) for decreased serotonergic activity in alcoholics, bulimics and possibly in opiate and psychostimulant abusers. It has been suggested that serotonergic deficiency may underlie drug-seeking behaviour and that brain serotonin activity contributes to satiety and modulates the reinforcing effects of drugs of addiction. Drugs which increase serotonergic activity, such as SSRIs, have a moderate therapeutic effect in reducing drug consumption in alcoholics, psychostimulant and opiate abusers (Ashton & Young, 1999). With regard to stress, Piazza and Le Moal (1998) review evidence that increased glucocorticoid secretion, or greater sensitivity to the effects of glucocorticoids (cortisol), either naturally present in certain individuals or induced by stress, increases vulnerability to pathological drug consumption, via enhancement of dopaminergic activity in reward areas of the brain. However, added to such biochemical variations are a whole host of psychological and sociological factors involved in addictive behaviour which are beyond the scope of this chapter (see Altman, 1998; Siegel, 1988).

7.2 Anxiety disorders

Stressful events, or events perceived by the individuals as dangerous or threatening, initiate a cascade of reactions which influence motivation and behaviour. Adaptive responses to acute threats include fight, flight, freezing in

some animals, followed by a learned avoidance in the future. One type of maladaptive response is state of anxiety which persists beyond the initial event. In humans this may include generalised anxiety, panic disorder, phobias, post traumatic stress disorder and obsessive compulsive disorder. These aversive reactions are closely connected (Tyrer, 1985). For example, repeated panic attacks, generated mainly in brainstem nuclei controlling autonomic reactions, encourage the development of a more generalised anticipatory anxiety, involving memory systems in limbic structures, especially hippocampus. Finally, learned strategies, involving prefrontal cortex, lead to avoidance behaviour such as agoraphobia (Gorman et al. 1989). Agoraphobia starting, for instance, as a panic attack in a supermarket, may become generalised so that the victim refuses to go out at all and becomes a virtual prisoner in his/her own home. This is surely a perversion of reward/punishment systems: the reward may be freedom from panic attacks (which becomes a dominant motivation) but the punishment is a self-imposed exile from society.

The brain systems involved in fear and anxiety have been described above. Neurotransmitter activity in panic and anxiety disorders is reviewed by Bell and Nutt (1998), Hamon (1994), Deakin et al. (1992) and Hood and Nutt (2000). Serotonin may play a dual role in promoting anticipatory anxiety but preventing panic (Deakin et al., 1992). Corticosteroids, released as part of the normal stress reaction, sensitise neurons in the ventral tegmental area to various stimuli, including the anxiogenic effects of amphetamine which appears to be separate from its psychostimulant effect (Hamon, 1994). GABA activity may be critically involved in anxiety disorders: there is evidence that drug-free patients with panic disorder have a deficiency in $GABA_A$ receptors, possibly leading to a deficit in inhibitory systems which normally control the paroxysmal elevations of anxiety seen in panic attacks (Hood & Nutt, 2000). In addition, a number of peptides, including CCK and CRF may be involved. The peptide CCK_4 has been shown to precipitate panic attacks in humans, regardless of diagnosis, but panic disorder subjects may have increased susceptibility (Hood & Nutt, 2000). CRF not only releases cortisone but may also induce anxiety-like behaviour in animals (Baldwin et al., 1990).

7.3 Depression and mania

Depression and mania are described in Chapter 16; they are mentioned here because of their close relation to reward and punishment systems. The passive anhedonia of melancholia, with inability to derive pleasure from usual enjoyments and general lack of motivation, indicates underactivity in reward

systems. The accompanying feeling of unworthiness and guilt suggests relative overactivity in reciprocally connected punishment systems. In contrast, mania and hypomania are characterised by elation and extravagantly optimistic behaviour, suggesting overactivity in reward systems, unrestrained by any thoughts of punishment.

Willner (1995) provides evidence from many sources that increases or decreases of dopaminergic activity in the mesolimbic system may underpin the pathophysiology of mania and depression respectively. A key area involved may be the subgenual prefrontal cortex which receives extensive reciprocal dopaminergic projections from the ventral tegmental area and substantia nigra and influences dopamine release in the nucleus accumbens (Drevets et al., 1997; see Chapter 16).

7.4 Chronic pain syndromes

Acute pain is clearly adaptive in preventing or minimising tissue injury; pain persisting for a while after injury may also serve a useful function in enforcing rest and promoting recovery. But chronic, unremitting pain, whether organic or psychogenic in origin, performs no such function and is usually maladaptive. Intense, long-continued pain dominates the sensorium, interferes with thought processes, undermines morale and may disorganise every body function (Sternbach, 1989; Chapman & Gavrin, 1999). There is increasing preoccupation with the symptom of pain which gradually comes to dominate consciousness, and motivation to recover or adapt seems to be lost.

The causes and mechanisms of chronic pain syndromes are diverse (Lance & McLeod, 1981). A similarity with depression has been noted by several authors and it has been suggested that chronic pain syndromes might result from reduced activity in serotonergic systems involved in pain suppression and mood control (Moldofsky, 1982). Other authors have suggested that a causative factor in chronic pain syndromes might be abnormally low concentrations or activity of endogenous opioids, particularly beta-endorphin (Lipman et al., 1990).

Of particular interest among the neurological causes of chronic pain is phantom limb pain, in which amputation or deafferentation of the limb (or other parts of the body) is regularly associated with persistence of the body image of the affected part. The phantom may be painless or painful and tends to shrink and eventually disappear over time. However, in about 50% of patients a painful phantom persists. The pain may be perceived in discrete parts of the phantom which may seem to move or feel as if fixed in a distorted position.

Central mechanisms of phantom pain are discussed by Melzack (1990), Harris (1999) and Ramachandran and Hirstein (1998) who postulate that phantoms originate from abnormal activity in widely distributed neural networks in the brain, containing a full sensory respresentation of the body. The sensory neuromatrix is closely linked to a representation of 'self' (a basic element of consciousness). Thus phantoms are always felt to be real and are clearly identified with self, "even when a phantom foot dangles in 'mid-air' (without a connecting leg) a few inches above the stump" (Melzack 1990). Such perception of self is in marked contrast to the syndrome of unilateral neglect seen in lesions of the right parietal lobe of the cortex, in which parts of the body are perceived as foreign and extraneous from the self. The phantom image is remarkably durable and persists after excision of large parts of the brain including somatosensory cortex and thalamus. Similar resistance to surgical ablation is shown by memory (Lashley, 1950) and in a sense a phantom *is* a memory, in which pain sensation can presumably be perpetuated by a variety of overlapping and versatile neural networks (Chapter 1), probably involving many neurotransmitters.

8.   Summary and conclusions

Reward and punishment systems are central to motivation, a key domain of consciousness (Chapter 13). They guide behaviour towards adaptive fulfilment and away from harm. In doing so they generate moods and emotions which often, if not always, reach conscious awareness, sometimes overpowering rational thought. Rewarding events elicit a range of pleasurable feelings (joy, contentment, hope, repletion) and aversive events a range of unpleasant feelings (hunger, thirst, pain, fear, disgust, guilt, despair). Omission of expected rewards or punishments provokes yet other emotions (disappointment, relief). The various neurotransmitters involved (monoamines, acetyl choline, peptides and many others) interact in complex ways and through different interconnected pathways, which are also bound up with learning and memory and with activity in arousal systems (Table 2). The sensitivity or responsiveness of reward and punishment systems to external and internal events differs between individuals and is important in determining personality characteristics and vulnerability to psychiatric disorders such as drug addiction, anxiety states, depressive disorders and chronic pain syndromes.

References

Altman, J. et al. (1996). *Psychopharmacology* 125, 285–345.

Ashton, C.H. & A.H. Young (1999). In S.C. Stanford (Ed.), *SSRIs: Past, Present, and Future* (67–91). Austin, Texas, USA: R.G. Landes Co.

Baldwin, H.A. et al. (1990). In D. Ganten & D. Pfaff (Eds.), *Behavioral Aspects of Neuro-endocrinology* (1–14). Berlin: Springer Verlag.

Bejerot, N. (1980). In D.J. Lettieri, M. Sayers & H.W. Pearson (Eds.), *Theories on Drug Abuse*. (246–255). Dept. of Health and Human Services, National Institute of Drug Abuse, Rockville, Maryland.

Bell, C.J. & D.J. Nutt (1998). *British Journal of Psychiatry* 172, 465–471.

Blackburn, J.R. et al. (1989). *Behavioural Neuroscience* 103, 15–23.

Bolles, R.C. & M.S. Fanselow (1982). *Annual Review of Psychology* 33, 87–101.

Brown, R.G. & G. Pluck (2000). *Trends in Neurosciences* 23, 412–417.

Chaouloff, F. (2000). *Journal of Psychopharmacology* 14, 139–151.

Chapman, C.R. & J. Gavrin (1999). *Lancet* 353, 2233–2237.

Charney, D.S. et al. (1995). In F.E. Bloom & D. Kupfer (Eds. *Psychopharmacology: The Fourth Generation of Progress*. (387–396). New York: Raven Press.

Cloninger, C.R. (1994). *Current Opinions in Neurobiology* 4, 266–273.

Cooper, S.J. (1984). *Trends in Pharmacological Sciences* 5, 49–50.

Deakin, J.F.W. et al. (1992). In C.A. Marsden & D.J. Heal (Eds.), *Central Serotonin Receptors and Psychotropic Drugs* (147–174). Oxford: Blackwell Scientific Publications.

Di Chiara, G. (1995). *Drug and Alcohol Dependence* 38, 95–137.

Di Chiara, G. & A. Imperato (1988). *Proceedings of the National Academy of Sciences, U.S.A.* 85, 5274–5278.

Di Chiara, G. & R.A. North (1992). *Trends in Pharmacological Sciences* 13, 185–193.

Dickenson, A.H. (1990). *Trends in Pharmacological Sciences* 11, 307–309.

Dourish, C.T. et al. (1986). *Trends in Pharmacological Sciences* 7, 212–215.

Drevets, W.C. et al. (1997). *Nature* 386, 824–827.

Drevets, W.C. et al. (2001). *Biological Psychiatry* 49, 81–96.

Dubner, R. & M.A. Ruda (1992). *Trends in Neurosciences* 15, 96–103.

Edelman, G.M. & G. Tononi (2000). *Consciousness: how matter becomes imagination*. London: Allen Lane.

Elde, R. et al. (1976). *Neuroscience* 1, 349–352.

Fitzgerald, M. (1986). *Trends in Pharmacological Sciences* 7, 51–52.

Gorman, J.M. et al. (1989). *American Journal of Psychiatry* 146, 148–161.

Gray, J.A. (1982). *The Neuropsychology of Anxiety*. Oxford: Clarendon Press, and New York: Oxford University Press.

Greenfield, S.A. (2000). *The Private Life of the Brain*. London: Allen Lane, The Pergamon Press.

Hamon, M. (1994). *Trends in Pharmacological Sciences* 15, 36–39.

Harris, A.J. (1999). *Lancet* 354, 1464–1466.

Hartvig, P. et al. (1989). *Trends in Pharmacological Sciences* (Suppl.) 75–79.

Heath, R.G. (1964). In RG Heath (Ed.), *The Role of Pleasure in Behaviour*. New York: Harper and Row.

Hood, S. & D. Nutt (2000). *Central Nervous System* 2, 7–10.

Hughes, J. (1983). *British Medical Bulletin* 39, 17–24.

Ikemoto, S. & J. Panksepp (1999). *Brain Research Reviews* 31, 6–41.

Kapp, B.S. & M. Gallagher (1979). *Trends in Neurosciences* 2, 172–180.

Koob, G.F. (1992). *Trends in Pharmacological* Sciences 13, 177–184.

Koob, G.F. & M. Le Moal (1997). *Science* 278, 52–58.

Lance, J.W. & J.G. McLeod (1981). *A Physiological Approach to Clinical Neurology.* London: Butterworth.

Lashley, K.S. (1950). *Symposia Society for Experimental Biology* 4, 454–482.

Le Moal, M & H.Simon (1991). *Physiological Reviews* 71, 155–234.

Levitt, R.A. & D.J. Lonowski (1975). In R.A. Levitt (Ed.), *Psychopharmacology: A Biological Approach* (51–91). Washington DC: Hemisphere Publishing Corporation.

Lipman, J.L. et al. (1990). *Psychopharmacology* 102, 112–116.

Mansour, A. et al. (1988). *Trends in Neurosciences* 11, 308–314.

Melzack, R. (1990). *Trends in Neurosciences* 13, 88–92.

Melzack, R. & P. Wall (1988). *The Challenge of Pain.* London: Penguin Books.

Mishkin, M. & T. Appenzeller (1987). *Scientific American* 256, 62–71.

Moldofsky, H. (1982). *Advances in Neurology* 33, 51–57.

Nutt, D.J. (1996). *Lancet* 347, 31–36.

Olds, J. & P. Milner (1954). *Journal of Comprehensive Physiology & Psychology* 47, 419–427.

Olds, M.E. & J. Olds (1963). *Journal of Comprehensive Neurology* 120, 259–262.

Panksepp, J. (1981). In S.J. Cooper (Ed.), *Theory in Psychopharmacology Vol. 1* (149–176). London: Academic Press.

Phillips, A.G. & H.C. Fibiger (1989). In J.M. Lieberman & S.J. Cooper (Ed.), *The Neuropharmacological Basis of Reward* (66–105). Oxford: Clarendon Press.

Piazza P.V. & M. Le Moal (1998). *Trends in Pharmacological Sciences* 19, 67–74.

Piomelli, D. et al. (2000). *Trends in Pharmacological Sciences* 21, 218–224.

Ramachandran, V.S. & W. Hirstein (1998). *Brain* 121, 1603–1630.

Redgrave, P. & P. Dean (1981). *British Medical Bulletin* 37, 141–146.

Redmond, D.E. (1987). In H.Y. Meltzer (Ed.), *Psychopharmacology: the Third Generation of Progress* (967–975). New York: Raven Press.

Routtenberg, A. (1978). *Scientific American* 239, 125–131.

Schaefer, J.G. & R.P. Michael (1990). *Psychopharmacology* 102, 263–268.

Schultz, W. et al. (1997). *Science* 275, 1593–1599.

Self, D.W. (1998). *Annals of Medicine* 39, 379–389.

Sepinwall, J. & L. Cook (1979). *Federation Proceedings* 39, 3024–3031.

Siegel, S. (1988). In M. Lader (Ed.), *Psychopharmacology of Addiction* (73–96). Oxford: Oxford University Press.

Spanagel, R. & F. Weiss (1999). *Trends in Neurosciences* 32, 521–527.

Stein, L. (1968). In D.H. Efron (Ed.), *Psychopharmacology—A Review of Progress 1957–1967.* Publ. No. 1836, (105–123). Washington DC: US Government Printing Office.

Stein, L. (1971). *Journal of Psychiatric Research* 8, 345–361.

Stein, L. (1978). In M.A. Lipton, A. DiMascio & K.F. Killam (Eds.), *Psychopharmacology: A Generation of Progress* (569–581). New York: Raven Press.

Stein, L. & Belluzi, J.D. (1988). In M.L. Commons, R.M. Church, J.R. Stellar, & A.R. Wagner (Eds.), *Quantitative Analysis of Behavior, Vol. 7, Biological Determinants of Reinforcement and Memory* (249–264). Hillsdale, New Jersey: Lawrence Erlbaum Associates.

Stein, L. & J.D. Belluzi (1989). *Neuroscience and Biobehavoural Reviews* 13, 69–80.

Stein, L. & C.D. Wise (1969). *Journal of Comprehensive Physiology & Psychology* 67, 189–198.

Stein, L. & C.D. Wise (1974). *Advances in Biochemical Psychophysiology* 11, 281–291.

Sternbach, R.A. (1989). In P.D. Wall & R. Melzack (Eds.), *Textbook of Pain* (242–245). Edinburgh: Churchill Livingstone.

Strang, J. et al. (1993). In C. Hallstrom (Ed.), *Benzodiazepine dependence* (128–142). Oxford: Oxford University Press.

Thompson, J.W. (1984). *British Medical Journal* 288, 259–261.

Tyers, M.B. & A.G. Hayes (1992). In C.A Marsden & D.J. Heal (Eds), *Central Serotonin Receptors and Psychotropic Drugs* (292–305). London: Blackwell Scientific Publications.

Tyrer, P.J. (1985). *Lancet* i, 685–688.

Valentino, R.J. & G.S. Aston-Jones (1995). In F.E. Bloom & D. Kupfer (Eds.), *Psychopharmacology: The Fourth Generation of Progress* (373–386). New York: Raven Press.

Villareal, J.E. & L.A. Salazar (1981). In F. Hoffmeister & S. Stille (Eds.), *Psychomotor Agents, Part II* (607–635). Heidelberg: Springer-Verlag.

Volkow, N.D. et al. (1999). *Journal of Psychopharmacology* 13, 337–345.

Wickelgren, I. (1997). Getting the brain's attention. *Science* 278, 35–37.

Willner, P. (1995). In F.E. Bloom & D.J. Kupfer (Eds.), *Psychopharmacology: The Fourth Generation of Progress* (921–933). New York: Raven Press.

Wise, R.A. & M.A. Bozarth (1987). *Psychological Reviews* 94, 469–492.

Yaksh, T.L. & L.D. Aimone (1989). In P.D. Wall & R. Melzack (Eds.), *Textbook of Pain* (181–205). Edinburgh: Churchill Livingstone.

Sleep

Slow wave and non-REM stages

Ann L. Sharpley

1. Introduction

Sleep involves a global alteration of brain functioning, occupies one third of our lives, and still retains many of its mysteries, particularly with respect to the function of sleep. The transition from waking to non rapid eye movement (non-REM) sleep is one of the most dramatic natural alterations in consciousness. This reduction in conscious awareness appears to be essential: non-REM sleep deprivation affects both cognitive and body functioning (Horne, 1988); conversely, quiet waking does not satisfy the need for sleep. Slow wave sleep usually lasts for 70–90 minutes and takes place during the first hours of sleep, as though it were essential to ensure this stage. It has been suggested that slow wave activity (SWA) is necessary for replenishment of cerebral glycogen stores that are depleted during waking (Benington et al., 1995). According to this hypothesis, adenosine release is the feedback signal whereby depletion of cerebral glycogen stores results in increased sleep requirement. This model explains the necessity of the key phenomena of non-REM sleep that distinguish it from waking: reduction in neuronal responsiveness, inattention to sensory stimuli, and loss of consciousness (Benington et al., 1995). This is an exciting period for basic sleep research as mechanisms controlling changes in sleep and wakefulness are progressively identified.

2.   Sleep structure

2.1   Electroencephalogram (EEG) measurements

Historically, and until the recent advent of in vivo neuroimaging, EEG measurements have been central to the study of alterations in consciousness associated with sleep. Sleep EEG recordings were first described in 1937 (Loomis et al., 1937). However, it was not until 1953 that the occurrence of binocularly synchronous eye movements during sleep in humans was observed (Aserinsky et al., 1953). Regular cyclic variations of the EEG, eye movements and body movements with a period of about 90–100 minutes throughout the night were then reported (Dement et al., 1957). Moreover, the peaks of eye and body movements coincided with the lightest phase of the EEG cycles and individuals maintained a very striking regularity in their sleep pattern from night to night.

Over the next few years, research into sleep gained momentum. REM sleep was identified in cats and thus found not to be unique to humans (Dement, 1958). Muscle tone was noted to be high during slow wave sleep (SWS) but suppressed during REM sleep (Jouvet et al., 1959). It was at this time that sleep was first thought of as being composed of REM sleep and non-REM sleep, rather than being a unitary state (Jouvet, 1962; Oswald, 1962). These two states differ fundamentally in most physiological parameters including the activity of a variety of key neurotransmitter systems.

As sleep studies intensified, it became clear that laboratories were not using the same criteria to measure sleep stages (Monroe, 1969). A committee of founders of sleep medicine research was established, chaired by Rechtschaffen and Kales, to standardise criteria for sleep staging. Sleep was scored in small segments known as epochs (usually 30 seconds). The stages described were wakefulness, movement time, stages 1 to 4 (non-REM sleep) and REM sleep. The dominant sleep stage was determined for each epoch using the criteria, defined by the committee (Rechtschaffen & Kales, 1968), which are still used today. The availability of digital recordings and computer-assisted interpretation now make it possible to analyse sleep as a more continuous process. Amongst these newer approaches are spectral analysis (Philip-Joet et al., 1993), fast Fourier transform (Albertario et al., 1995) and pattern recognition using an artificial neural network (Pardey et al., 1996).

A relationship exists between EEG patterns and the level of vigilance and consciousness. The states of wakefulness and sleep are characterised by three physiological correlates: brain wave activity (electroencephalogram, EEG), eye movements (electro-oculogram, EOG) and muscle tone (electromyogram,
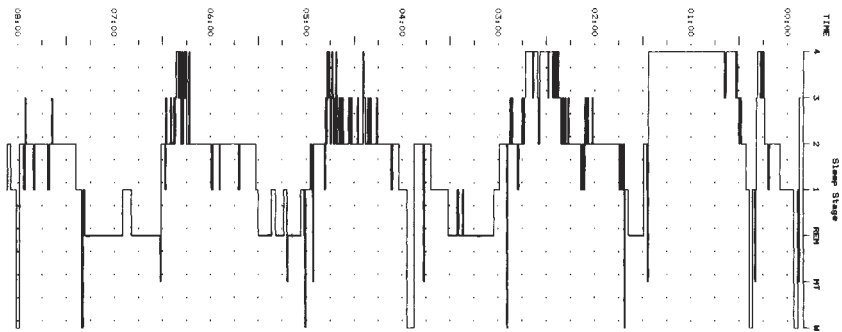
Figure 1. Sleep (non-REM).

EMG). There is a progressive increase in the stimulus threshold necessary to produce arousal from stage 1 through stage 2 and stages 3 and 4 slow wave sleep (SWS). During SWS, noise stimuli that are sub-threshold for arousal may not cause any EEG pattern alterations. A typical and predictable progression occurs from one sleep stage to another during the night (Fig. 1). Body movements tend to cluster just before and during REM sleep. Although dreams are closely associated with REM sleep, they also occur although less vividly during SWS. A study of sleep onset (hypnagogic) mentation found that the longer subjects had been asleep before awakening (from 5 seconds to 5 minutes) the less mentation (fewer thoughts) was reported, but the greater was the number of unusual thoughts including visual hallucinations (Rowley et al., 1998).

2.2 Active wakefulness

Active wakefulness is accompanied by low-amplitude ($<10\,\mu V$), high frequency (>13 Hz) beta waves in the EEG. During waking, thalamocortical cells are in a state of tonic depolarisation with relatively stable membrane potentials of around -60 mV (Coenen, 1998). Neurons fire in a 'tonic' or 'relay' mode, implying a sustained and spontaneous activity (Glenn et al., 1982). This variable discharge pattern with a low synchronisation between cells is the reason EEG electrodes, which sum up the electrical activity of numerous cells, record small but irregular waves with a high frequency of fluctuation. The tonic mode of firing is the substrate of beta waves. In relaxed wakefulness with eyes closed, the EEG is typified by alpha (8–12 Hz) intermixed with beta. Some individuals have a virtually continuous alpha record, while others may show little or none. Eye movements are often present and the EMG is generally high. As
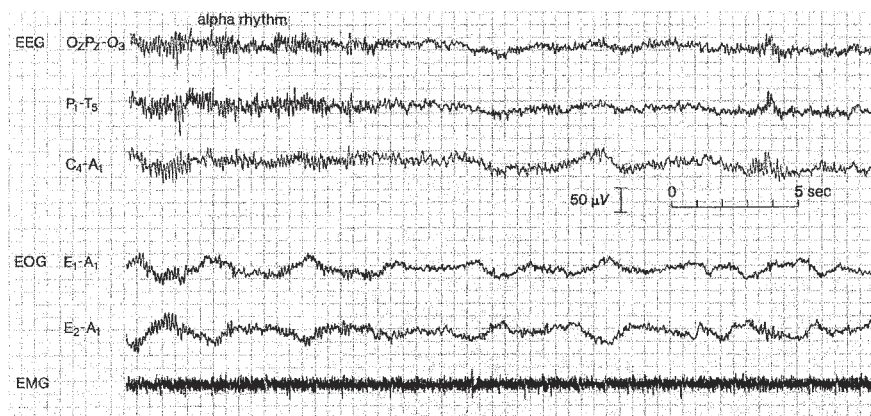
Figure 2. Awake activity.

an individual becomes drowsy, alpha decreases and the eyes may begin to roll (Fig. 2).

2.3 Stage 1 sleep

The change from relaxed wakefulness to stage 1 is characterised by a general slowing of activity (mixed frequency beta and theta (3.5–7.5 Hz)) and a decrease in alpha (to <50%). Slow rolling or horizontal eye movements are often present, each of several seconds duration, and the EMG is generally lower than during relaxed wakefulness. Stage 1 generally occurs in the transition from wakefulness to sleep, and following movements. Subjects in stage 1 can be easily aroused. Stage 1 occupies between 2–5% of sleep. If aroused, subjects usually describe being half-awake rather than asleep. A phasic EEG waveform known as vertex sharp waves may be present, usually in theta range frequency (Fig. 3). Vertex sharp waves are maximal at the vertex and negative in relation to other areas, often associated with arousal stimuli. The amplitude is variable (up to 300 μV) and is maximal in children.

2.4 Stage 2 sleep

Stage 2 sleep is composed of a largely theta background, with the intermittent appearance of K-complexes (so named because of their morphological resemblance to this letter) and sleep spindles (Fig. 4). Stage 2 occupies about 50% of sleep. K-complexes are negative waves followed 0.75 seconds later by a positive
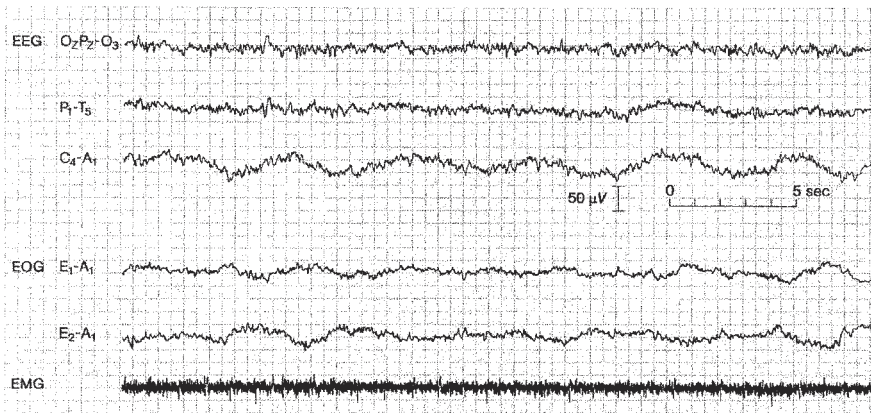
Figure 3. Stage 1 (drowsy sleep).
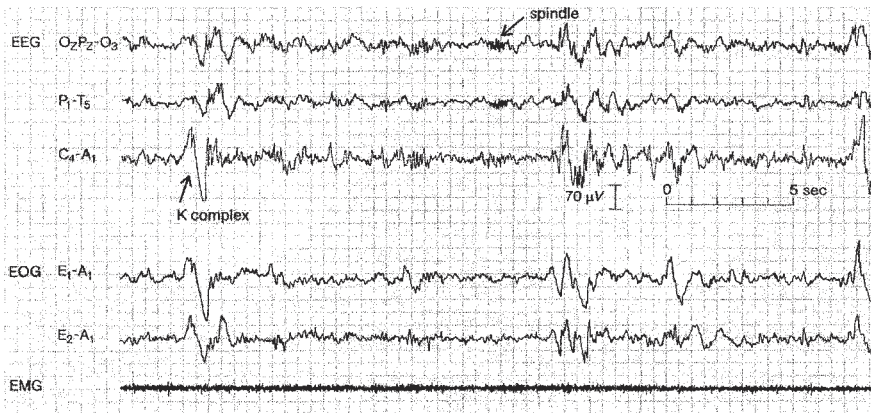
Figure 4. Stage 2 sleep.

wave. The amplitude is variable but usually about 200 μV and is maximal at the vertex. This is often followed by a spindle which is an episodic brief burst of low amplitude, high frequency (12–14 Hz) activity with a wave amplitude that waxes and wanes over the spindle duration of 0.5–1.5 seconds. Spindles are of thalamic origin and are probably associated with a blockade of synaptic transmission of afferent impulses through the thalamus and indicate loss of consciousness (Mulle et al., 1986). K-complexes may occur either spontaneously or in response to a sudden, external, sensory stimulus. It has also been suggested that K-complexes occur when there is a change in autonomic system activity (e.g. gut or bladder contractions) (Johnson et al., 1968). Meaningful

auditory stimuli (e.g. the subject's name), provoke K-complexes more readily than meaningless stimuli (Oswald, 1962). Two to three K-complexes occur per minute in stage 2 sleep.

2.5 Slow wave sleep (SWS) (stages 3 and 4)

SWS is characterised by high amplitude ($>75\ \mu V$) and low frequency (<3.5 Hz) delta waves (Fig. 5). SWS occupies approximately 20% of sleep. Stage 3 is scored when at least 20% but not more than 50% of the epoch consists of delta waves. Stage 4 is scored when more than 50% of the epoch consists of delta waves. Most stage 4 epochs have the appearance of being completely dominated by this activity. Delta waves appear when neurons undergo further hyperpolarisation to about -70 to -90 mV. The increase in amplitude implies that extended populations of neurons fire more synchronously, interspersed with prolonged hyperpolarisations. Inhibitory interneurons play a role in the lowering of the membrane potential of the relay cells; they are also responsible for the strong synchronisation of these cells by linking them together by powerful inhibitory activities. Delta waves are irregular and this mode of activation results in pause-burst discharges of many cells, known as 'burst' mode (Nunez et al., 1992). Delta waves represent thalamocortical oscillations occurring in the absence of activating or arousing inputs. As SWS terminates, the reverse occurs and thalamocortical cells begin to depolarise. At this point, REM sleep normally begins. However, arousal disorders can manifest themselves if behavioural arousal from SWS occurs in the presence of continued delta.
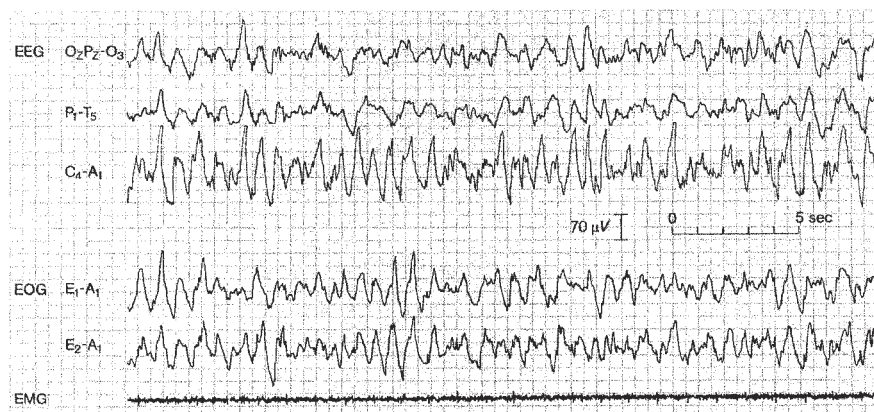
Figure 5. Slow wave sleep.

3.   Neuroanatomy

A detailed description of the neuroanatomical structures involved in sleep is provided in the excellent reviews, of Jones (1989) and Hobson et al. (1998). Alertness and sleep are dependent on the activity of the brain as a whole, although different levels of consciousness are determined primarily by areas of the brain stem. Lesion and stimulation studies have been used to identify specific regions and delineate relevant neuronal systems (reviewed by Parkes, 1985).

The cortex is essential for the normal regulation and maintenance of non-REM sleep and wakefulness although, in anencephalic human infants, sleep and waking does occur even with a totally absent cerebral cortex (Puech et al., 1947). The cortex can activate the reticular formation, resulting in turn in activation of the cortex and a general arousal response (Bremer et al., 1953). The cerebellum is involved with the control of movements and posture during wakefulness and sleep (Fadiga et al., 1968). However, cerebellectomy results in little modification of the sleep-wake cycle. Lesion studies show that sleep may occur in the absence of the thalamus, but sleep spindles are abolished (Bricola, 1968). A study of cerebral regional blood flow (rCBF) during SWS has shown that thalamic rCBF decreases dramatically as a function of delta and spindle activity (Hofle et al., 1997).

The posterior, lateral and medial hypothalamus is a continuation of, and is closely related to, the ascending activating reticular system (Passouant, 1967). Clinical evidence in man shows that lesions of the posterior hypothalamus produce sleepiness. Moreover, depending on the exact site as well as the extent of the lesion, hypersomnia, coma or changes in the circadian rhythmicity of sleep results (Parkes, 1985). Conversely, lesions of the anterior hypothalamus results in insomnia (von Economo, 1930).

A key neuroanatomical structure in the regulation of waking and sleeping, and thus consciousness, is the reticular formation, located in the brain stem. This is a highly complex interlacing network of fibre bundles (Olszewski, et al., 1954). Neurochemically, there is a great diversity of neurotransmitters present: serotonin, mainly from the mid-line raphe nuclei; noradrenaline from the locus coeruleus; acetylcholine from pedunculopontine nuclei (see also Chapters 1 and 2); with also peptidergic (Ljungdahl et al., 1978) and dopaminergic components (Hartman et al., 1982). With complete lesioning of the raphe system, animals remain awake, unable to sleep; with partial lesions, SWS is selectively abolished (Morgane et al., 1973). Electrical stimulation of the locus coeruleus area always induces wakefulness (Fredrickson et al., 1970). It can be

concluded from anatomical studies that the integrity of much of the brainstem and the cerebral cortex is required for normal sleep patterns. The sleep wake rhythm itself seems to arise in the whole brain, the cerebrum as well as the brain stem, as shown by the recovery (although often slow and incomplete) from coma in humans with high brain stem lesions (Parkes, 1985). Hypothalamic and midline thalamic areas may be important for determining pre-sleep behaviour; whilst sleep onset itself is likely to be determined by a suprachiasmatic internal pacemaker and withdrawal of the influence of the ascending reticular system (Parkes, 1985).

Sleep studies using positron emission tomography (PET) have demonstrated that cerebral metabolic rates for glucose decrease during SWS compared with wakefulness (Maquet, 1995; Maquet, 1997; Hofle et al., 1997; Hobson et al., 1998). During REM sleep, cerebral glucose metabolism is as high as during wakefulness. During slow wave sleep the most deactivated areas are the upper brainstem, thalamic nuclei and basal forebrain and deactivation of the basal ganglia also occurs. In the cortex, the least active areas are the associative cortices of the frontal and parietal cortex (Maquet, 1999). State-dependent changes in the activity of regions, including the brainstem, thalamus and basal forebrain (deactivations during SWS and reactivations during REM sleep) are consistent with the idea that these areas mediate arousal (Braun et al., 1997). Deactivation of the heteromodal association areas (the orbital dorsolateral prefrontal and inferior parietal cortices) constitute the single feature common to both non-REM and REM sleep states, and may be a defining characteristic of sleep itself (Braun et al., 1997).

4.   Neurochemistry

The alterations in neurotransmitter activity which trigger or accompany the onset of natural sleep and distinguish slow wave or non-REM from REM sleep, provide one of the most compelling arguments in favour of chemical neurotransmission being specifically involved in mechanisms of conscious awareness. For an extensive review on neurochemistry and sleep, see Gottesman (1999).

4.1 Adenosine

The inhibitory neuromodulator, adenosine, is considered to be a major candidate for a sleep-inducing factor. Systemic or intracerebroventricular injec-

tions of adenosine promote sleep and decrease wakefulness (Ticho et al., 1991; Radulovacki, 1985). Conversely, adenosine receptor antagonists caffeine and theophylline are widely used as stimulants to induce vigilance and promote wakefulness (Fredholm, 1995). Caffeine suppresses EEG power density in the low frequencies and enhances power density in the frequency range of sleep spindles, changes which are opposite to those observed after sleep deprivation (Landolt et al., 1994).

During sleep deprivation, adenosine levels increase significantly in the cholinergic region of the basal forebrain and to a lesser extent in the cortex but not in other regions such as thalamus, hypothalamus, dorsal raphé nucleus or pedunculopontine tegmental nucleus (Porkka-Heiskanen et al, 2000). It has been hypothesised that adenosine accumulates in the extracellular space of the basal forebrain during wakefulness (Porkka-Heiskanen et al., 1997) and that this increases sleep propensity. The increase in extracellular adenosine concentration decreases the activity of the wakefulness-promoting cell groups, in particular cholinergic neurons in the basal forebrain. When the activity of the wakefulness-active cells decreases sufficiently sleep is initiated. During sleep the extracellular adenosine concentrations decrease, and thus the inhibition of the wakefulness-active cells also decreases allowing the initiation of a new wakefulness period (Portas et al., 1997; Porkka-Heiskanen et al., 1997). The A1 receptor antagonist cyclopentyltheophylline applied to the basal forebrain decreases slow wave sleep and increases wakefulness (Strecker et al., 2000).

4.2 Dopamine

Dopaminergic neurons in the ventral tegmental areas are constantly active throughout the various stages of sleep, including SWS or non-REM. Lesions in the major dopamine systems cause minor alterations in sleep. D-amphetamine, methylphenidate, high doses of L-dopa and cocaine, which predominantly enhance dopamine activity, induce arousal and decrease REM sleep (Gillin et al., 1978). An increase in dopamine activity following activation of postsynaptic D_2 receptors or blockade of presynaptic D_2 receptors produces an increase in wakefulness (Monti et al., 1988).

4.3 Histamine

Ascending histamine containing fibres originating from the reticular formation are considered important in arousal. Histaminergic neurons cease firing with the onset of sleep. Histamine antagonists (for the treatment of allergies) are

often used as 'over the counter' sleep inducing medication. H_1 antagonists impair daytime vigilance (Nicholson et al., 1985) and the H_1 antagonist, mepyramine, has specifically been shown to cause sedation and decrease wakefulness (Solomon et al., 1989).

4.4 Noradrenaline

Locus coeruleus noradrenergic neurons decrease their rate of firing at sleep onset. Drugs that diminish noradrenergic neurotransmission at post-synaptic α-1 adrenoceptors tend to cause sedation, while the reverse is the case for drugs that potentiate noradrenergic function (Nicholson et al., 1986; Hilakivi et al., 1984). Noradrenergic neurons cease firing during REM sleep.

4.5 Acetylcholine

Cholinergic mechanisms are important in wakefulness and cortical activation (Datto et al., 1991). In general, increasing acetylcholine is associated with wakefulness and REM sleep and decreasing acetylcholine promotes sleep and non-REM sleep phenomena. Evidence implicating acetylcholine containing neurons in the peribrachial pons as critical in the triggering and maintenance of REM sleep (Hobson, 1992) is discussed further in Chapters 7 and 8. Although little is known about endogenous neuropeptide changes during the sleep-wake cycle, it has recently been shown that neurotensin injections in the basal forebrain decrease slow wake sleep and, remarkably in the virtual absence of slow wave sleep, increase REM sleep (Cape et al., 2000).

4.6 Serotonin

Recent microdialysis experiments provide evidence that the level of serotonin during waking is higher in most cortical and subcortical areas receiving serotonergic projections than during sleep (Portas et al., 2000). The neurons of the ascending raphe nuclei show the highest firing rate during waking, decrease their firing rate during SWS and become virtually silent during REM sleep (McGinty et al., 1976). This suggests that during waking serotonin may complement the action of noradrenaline and acetylcholine in promoting cortical responsiveness, and participates in the inhibition of REM-sleep effector neurons in the brainstem (Portas et al., 2000).

Administration of the inhibitor of 5-HT synthesis, para-chlorophenyl-alanine (PCPA), in cats causes insomnia which can be reversed by the 5-HT

precursor, 5-hydroxytryptophan (Wyatt, 1972). Studies indicate that 5-HT pathways and, in particular, the 5-HT$_{2A/2C}$ receptor, play a critical role in the regulation of SWS (Sharpley et al., 1994). For example, the 5-HT$_{2C}$ receptor antagonist, ritanserin, produces a substantial, dose-dependent increase in SWS in healthy volunteers (Idzikowski et al., 1987; Sharpley et al., 1990). Conversely, a decrease in SWS is noted with the 5-HT$_{2C}$ agonist meta chlorophenylpiperazine (mCPP) (Katsuda et al., 1993). Thus the present data suggest that 5-HT$_{2C}$ receptors may regulate SWS in humans. Serotonin is implicated in psychiatric disorders, particularly depression and anxiety (Chapters 5 and 18). Several antidepressant drugs, particularly, tricyclic antidepressants, mianserin and trazodone have a significant affinity for 5-HT$_2$ receptors and have been noted to increase SWS. In contrast, selective serotonin reuptake inhibitors (SSRIs) and monoamine oxidase inhibitors (MAOIs) do not increase SWS (for review see Sharpley et al., 1995).

4.7 Gamma-aminobutyric acid (GABA)

GABA receptors play an important role in the regulation of sleep (reviewed by Lancel, 1999). GABA is the major inhibitory neurotransmitter in the central nervous system and its depressant actions are predominantly mediated by GABA$_A$ receptors (Bloom et al., 1971). GABA$_A$ receptors possess additional allosteric binding sites, including sites for barbiturates, benzodiazepines, zolpidem, zopiclone and neuroactive steroids (Sieghart, 1995). These compounds facilitate inhibitory synaptic transmission at GABAergic synapses by increasing the affinity of the GABA receptor, and increasing the likelihood of chloride channel opening (Haefely et al., 1975). Sleep effects include increased ability to fall and remain asleep, increased stage 2 sleep and an increased appearance of spindles within stage 2 sleep. SWS and REM sleep are suppressed. Spindle waves arise as the result of interactions between spindle pacemaker GABAergic neurons in the nucleus reticularis (RE) of the thalamus and thalamocortical neurons (Steriade et al., 1990). Spindles are blocked by brainstem cholinergic neurons that synapse in the thalamus. The forebrain nucleus basalis also provides depolarising cholinergic and hyperpolarising GABAergic input to the RE that assists brainstem input in disrupting spindling activity (Sinton et al., 2000). In addition, during deprived slow wave sleeps there is a correlation between increased GABA neuron slowing in the ventral tegmental area and increased delta/power (Lee et al., 2001).

5.   Parasomnias

A variety of phenomena can emerge from non-REM sleep, which are considered as arousal disorders, occurring in normal individuals. A neurochemical basis for some of these is indicated by relevant drug effects.

5.1   Somniloquy (sleep talking)

Somniloquy (sleep talking) is a common parasomnia that ranges from mumbled nonsense to coherent sentences, but without detailed awareness of the event. Sleep talking can occur in all stages of sleep but is frequently observed soon after sleep onset. It is usually an isolated phenomenon, in otherwise healthy individuals. Important precipitants include emotional stress and febrile illness. It is also a feature of obstructive sleep apneoa syndrome. Although present in some adults it is most common in children and teenagers (Arkin, 1966). In a recent study in bilingual sleep talkers (sleep talking present in 56.3% of sample) it was found that most children used their dominant (i.e. native) language during sleep. Interestingly, a minority (<4%) used their non-dominant language (Pareja et al., 1998).

5.2   Bruxism (tooth grinding)

Bruxism mainly occurs in stage 2 sleep and REM sleep (Bader et al., 1977). A relationship to stress and anxiety has been suggested, but the disorder can be chronic without apparent association with stress (Faulkner, 1990; Pierce et al., 1995). It has been suggested that the central dopaminergic system may be involved in the modulation of sleep bruxism (Lobbezoo et al., 1997). Case reports indicate that bruxism can be induced by the SSRI paroxetine (Romanelli et al., 1996). The mechanism remains unclear; possibilities include sleep disturbance, serotonergic-mediated inhibition of dopamine manifesting as akathisia, and SSRI-induced anxiety. SSRI-induced bruxism may respond to therapy with buspirone (Ellison et al., 1993).

5.3   Somnambulism (sleep walking)

Somnambulism (sleep walking) is a disorder of arousal that often includes complex, wake-like behaviour with an unclear connection to conscious intention (Whyte, 1989). Onset of this disorder usually occurs in childhood from the age of three and often remits spontaneously with puberty (Rosen et al., 1995;

Keefauver et al., 1994). It is surprisingly common. Prevalence rates have been estimated at 20% of children (aged 3–15), although this incidence rises to 60% if both parents have a history of arousal disorders and 2.5% of adults (Kales et al., 1980). Episodes often cluster in time, and evidence exists that these events are most probable during those nights when heightened sleep pressure (e.g. from prior sleep deprivation or irregular sleep patterns) combines with factors that tend to fragment sleep (emotional stress or pain) (Broughton, 1991). Typically, somnambulism occurs during SWS, approximately 1 hour after sleep onset, at the time when the first REM episode would be expected. Somnambulism may reflect an immaturity in the control mechanisms that gate forebrain arousal into REM sleep at the end of SWS (Sinton et al., 2000). A deepened or enhanced sleep state could be a predisposing factor (Broughton, 1968). Case reports indicate that the amount of SWS is greater in somnambulistic individuals than would be expected based upon age-adjusted norms (Williams et al., 1974) and some may possess unusually high amplitude delta waves. This may suggest increased activity of the delta-sleep-generating mechanism (Whyte, 1989). In recent study of bipolar patients the prevalence of somnambulistic-like behaviour related to treatment with lithium alone or in combination with other psychotropic medications was examined (Landry et al., 1999). Seven per cent (27/389) reported somnambulistic behaviour related to the onset of treatment and a further 3% (12/389) had their childhood somnambulism reactivated by the medication. The results indicate a possible link between serotonin and somnambulism. Moreover, a further study (Barabas et al., 1984) found a high incidence (17%; 10/57) of somnambulism in children with Tourette syndrome, again indicating a possible link with serotonin.

During episodes of somnambulism, appetitive behaviours are unusual and, when they do occur, raise questions as to the true state of consciousness of the patient. Patients often report a conscious preoccupation with food or weight management. Three case reports in adults of nocturnal food consumption with polysomnography and video taping evidence strongly support a diagnosis of eating during somnambulistic state (Whyte, 1989). These patients experienced retrograde amnesia for the events, and knew that episodes had occurred only because evidence of eating was present in the morning. The consumption of unappetizing foods (e.g. raw bacon) suggests a state of impaired consciousness.

5.4 Pavor nocturnus (night terrors)

Pavor nocturnus (night terrors) is a further arousal disorder mainly of childhood emanating from SWS. Like somnambulism it usually remits in puberty

(Rosen et al., 1995). Prevalence rates have been estimated at 6% in children and 1% in adults. Night terrors occur during the first third of the night when the first REM episode would be expected. Typically, the child sits up, cries or screams with terror, and presents with intense anxiety accompanied by autonomic arousal, including polypnea, tachycardia, sweating, mydriasis and muscle hypertonia (Sinton et al., 2000). The attack rarely lasts more than 15 minutes. There is subsequent amnesia of the event. Although rare in adults, night terrors can lead to serious disruption of sleep resulting in impaired daytime functioning. In a case series of 6 patients, the SSRI paroxetine was found to be effective in the treatment of long standing and disabling night terrors (Wilson et al., 1997). It is suggested that the terror-suppressing action of paroxetine is a direct effect of its ability to increase serotonin in the brain stem by blocking reuptake. Night terrors recurred rapidly on cessation of paraoxetine, and restarting treatment quickly caused suppression. The effectiveness of paroxetine may suggest a role for decreased central 5-HT function in the aetiology of night terrors (Wilson et al., 1997).

5.5 Sleep-related violence

Sleep related violence has been documented in sleep walking, sleep terrors, in REM sleep behaviour disorder (RBD), bruxism, hypnic jerks, hypnagogic hallucinations, during epileptic discharges during sleep, and in confusional arousals (arising from obstructive sleep apneoa and dementia) (Ohayon et al., 1977). A much higher incidence of violence has been documented in males (Moldovsky et al., 1995). Two large population studies both indicated little evidence for any underlying psychopathology in the majority of individuals with sleep-related complex behaviors (Guilleminault et al., 1995; Moldovsky et al., 1995). However, sleep related violence or RBD is associated with Parkinson's disease, Lewy body dementia and several other pathologies (Comella et al., 1998). There is some evidence to suggest that wakefulness, non-REM sleep and REM sleep may occur simultaneously, in incomplete or mixed form or may oscillate rapidly, resulting in bizarre and previously difficult to explain clinical behaviours (Mahowald et al., 1991; Mahowald et al., 1992). Extremely complex acts can result from these mixed states with preservation of motor activity without conscious awareness of the observed behaviours. Sleep related violence is rarely recurrent (Guilleminault et al., 1995). Potent risk factors known to trigger sleep-related violence in at-risk individuals include marked sleep deprivation, major psychological stress and physical overexertion. An excellent series of papers on forensic medicine and sleep can be found in a special issue

of the journal 'Sleep' (Volume 18, 1995). The degree and nature of conscious awareness is crucial in determining if an individual is to be held legally responsible for their actions. A precedent was established by a case of homicidal somnambulism where a young man drove 23 kilometers and then stabbed his mother-in-law to death (Broughton et al., 1994). He was acquitted on the basis of somnambulism, which is regarded legally as a non-insane automatism with low probability of recurrence.

6. Conclusion

This chapter briefly reviews sleep structure, neuroanatomy, neurochemistry and parasomnias of non-REM sleep. It is well established that several neurotransmitters, neuropeptides and neurohormones are involved in the modulation of the sleep-wake cycle. In particular the elevation in adenosine levels, and concomitant reduction in cholinergic, serotonergic, noradrenergic and histaminergic neurotransmission appear to be specifically related to the sudden loss or major reduction in conscious awareness that occurs at the onset of sleep. Developing further understanding of unconsciousness during SWS or non-REM sleep and its relation to changing patterns of neurotransmitter activity, is likely to lead to understanding of consciousness (Flavell et al., 1999).

References

Albanese, A. & L.L. Butcher (1980). *Brain Research Bulletin* 5, 127–134.

Albertario, C.L. et al. (1995). *Sleep* 18, 836–843.

Arkin, A.M. (1966). *Journal of Nervous and Mental Disorders* 143, 101–122.

Aserinsky, E. & N. Kleitman (1953). *Science* 118, 273–274.

Bader, G.G. et al. (1977). *Sleep* 20, 982–990.

Barabas, G. et al. (1984). *Developmental Medicine in Childhood Neurology* 26, 457–460.

Benington, J.H. & H.C. Heller (1995). *Progress in Neurobiology* 45, 347–360.

Bloom, F.E. & L.L. Iversen (1971). *Nature* 229, 628–630.

Braun, A.R. et al. (1997). *Brain* 120, 1173–1197.

Bremer, F. & C. Terzuola (1953). *Journal of Physiology* 45, 56–67.

Bricola, A. (1968). *Proceedings of the XVth European Meeting on Electrophysiology.* Auto Gaggi, Bologna.

Broughton, R. (1968). *Science* 159, 1070–1078.

Broughton, R. (1991). *Phasic and dynamic aspects of sleep: a symposium, review and synthesis.* New York: Raven Press.

Broughton, R. et al. (1994). *Sleep* 17, 253–264.

Cape, E.G. et al. (2000). *Journal of Neuroscience* 20, 8452–8461.

Coenen, A.M.L. (1998). *Consciousness and cognition* 7, 42–53.

Comella, C.L. et al. (1998). *Neurology* 51, 526–529.

Datto, S. et al. (1991). *Neuroreport* 2, 619–622.

Dement, W. (1958). *Electroencephalography and Clinical Neurophysiology* 10, 119–131.

Dement, W. & N. Kleitman (1957). *Electroencephalography and Clinical Neurophysiology* 9, 673–690.

Ellison, J.M. & P. Stanziani (1993). *Journal of Clinical Psychiatry* 54, 432–434.

Fadiga, E. et al. (1968). *Electroencephalography and Clinical Neurophysiology* 24, 330–342.

Faulkner, K.D.B. (1990). *Australian Dental Journal* 35, 266–276.

Flavell, J.H. et al. (1999). *Child Development* 70, 396–412.

Fredholm, B.B. (1995). *News of Physiological Science* 10, 122–128.

Fredrickson, C.J. & J.A. Hobson (1970). *Archives of Italian Biology* 108, 564–576.

Gillin, J. et al. (1978). *Annual Review of Pharmacology and Toxicology* 18, 563–579.

Glenn, L.L. & M.S.O. Steriade (1982). *Journal of Neuroscience* 2, 1387–1404.

Gottesmann, C. (1999). *Progress in Neurobiology* 59, 469–508.

Guilleminault, C. (1995). *Sleep* 18, 740–748.

Haefely, W. (1975). *Advances Bichemical Psychopharmacology* 14, 131–151.

Hartman, B.K. (1982). *Brain Research* 240, 235–243.

Hilakivi, I. & A. Leppavuori (1984). *Acta Physiology Scandanavia* 120, 363–372.

Hobson, J.A. (1992). *Current Opinion in Neurobiology* 2, 759–763.

Hobson, J.A. et al. (1998). *Current Opinion in Neurobiology* 8, 239–244.

Hofle, N. (1997). *Journal of Neuroscience* 17, 4800–4808.

Horne, J. (1988). *Why we sleep*. Oxford: Oxford University Press.

Idzikowski, C. (1987). *Psychopharmacology* 93, 416–420.

Johnson, L.C. & W. Karpan (1968). *Psychophysiology* 4, 444–452.

Jones, B.E. (1989). In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine* (121–138). Philadelphia: WB Saunders Company.

Jouvet, M. (1962). *Archives Italian Biology* 100, 125–206.

Jouvet, M. & F. Michel (1959). *Comptes Rendus des Seeances de la Societe de Biologie et de ses filiales (Paris)* 153, 422–425.

Kales, A. et al. (1980). *British Journal of Psychiatry* 137, 111–118.

Katsuda, Y. et al. (1993). *Biological Psychiatry* 33, 49–51.

Keefauver, S.P. & C. Guilleminault (1994). In M. Kryger, T. Roth & W. Dement (Eds.), *Principles and practice of sleep medicine*. Philadelphia: Saunders.

Lancel, M. (1999). *Sleep* 22, 33–42.

Landolt, H.P. et al. (1994). *Journal of Sleep Research* 3, 137.

Landry, P. et al. (1999). *International Clinical Psychopharmacology* 14, 173–175.

Lee, R.S. et al. (2001). *Journal of Neuroscience* 21, 1757–1766.

Ljungdahl, A. (1978). *Neuroscience* 3, 861–943.

Lobbezoo, F. et al. (1997). *Journal of Dental Research* 76, 1610–1614.

Loomis, A.L. et al. (1937). *Journal of Experimental Psychology* 21, 127–144.

Mahowald, M.W. & C.H. Schenck (1991). *Sleep* 14, 69–79.

Mahowald, M.W. & C.H. Schenck (1992). *Neurology* 42, 44–52.

Maquet, P. et al. (1997). *Journal of Neuroscience* 17, 2807–2812.

Maquet, P.S.O. (1995). *Neurophysiology Clinical* 25, 342–350.

Maquet, P. (1999). *Journal of Psychopharmacology* 13, 525–528.

McGinty, D.J. & R.M. Harper (1976). *Brain Research* 101, 569–575.

Moldovsky, H. et al. (1995). *Sleep* 18, 731–739.

Monroe, L.J. (1969). *Psychophysiology* 5, 376–384.

Monti, J.M. et al. (1988). *Sleep Research 17*, S67.

Morgane, P.J. & W.C. Stern (1973). In J. Barchas & E. Usdin (Eds.) *Serotonin and Behaviour* (427–442). New York: Academic Press.

Mulle, C. et al. (1986). *Journal of Neuroscience* 6, 2134–2145.

Nicholson, A.N. & P.A. Pascoe (1986). *Neuropharmacology* 25, 1079–1083.

Nicholson, A.N. et al. (1985). *Neuropharmacology* 24, 245–250.

Nunez, A. et al. (1992). *Neuroscience* 48, 75–85.

Ohayon, M.M. et al. (1977). *Journal of Clinical Psychiatry* 58, 369–376.

Olszewski, J. & D. Baxter (1954). *The cytoarchitecture of the human Human Brain Stem*. Philadelphia: Lippincott.

Oswald, I. (1962). *Proceedings of the Royal Society of Medicine* 55, 910–912.

Oswald, I. (1962). *Sleeping and waking*. Amsterdam: Elsevier.

Pardey, J. et al. (1996). *Journal of Sleep Research* 5, 201–210.

Pareja, J.A. et al. (1998). *Sleep* 22, 243–247.

Parkes, J.D. (1985). *Sleep and its disorders.* Philadelphia: WB Saunders.

Passouant, P. (1967). *Reviews in Neurology* 116, 467–470.

Philip-Joet, F.F. et al. (1993). *Chest* 104, 336–339.

Pierce, C.J. et al. (1995). *Journal of Orofacial Pain* 9, 51–56.

Porkka-Heiskanen, T. et al. (1997). *Science* 276, 1265–1267.

Porkka-Heiskanen, T. et al. (2000). *Neuroscience* 99, 507–512.

Portas, C.M. et al. (2000). *Progress in Neurobiology* 60, 13–35.

Portas, C.M. et al. (1997). *Neuroscience* 79, 225–235.

Puech, P. (1947). *Reviews in Neurology* 79, 116–124.

Radulovacki, M. (1985). *Clinical Basic Pharmacology* 5, 327–339.

Rechtschaffen, A. & A. Kales (1968). *A manual of standardised terminology, techniques and scoring system for sleep stages of human subjects*. UCLA Brain Information Service/Brain Research Institute, Los Angeles.

Romanelli, F. et al. (1996). *Annals of Pharmacotherapy* 30, 1246–1248.

Rosen, G. et al. (1995). In R. Ferber & M. Kryger (Eds.), *Principles and practice of sleep medicine in the child.* Philadelphia: Saunders.

Rowley, J.T. et al. (1998). *Conscious Cognition* 7, 67–84.

Sharpley, A.L. & P.J. Cowen (1995). *Biological Psychiatry* 37, 85–98.

Sharpley, A.L. et al. (1994). *Neuropharmacology* 33, 467–471.

Sharpley, A.L. et al. (1990). *Psychopharmacology* 101, 568–569.

Sieghart, W. (1995). *Pharmacology Review* 47, 181–234.

Sinton, C. & R. McCarley (2000). *Seminars in Clinical Neuropsychiatry* 5, 6–19.

Solomon, R.A. et al. (1989). *Journal of Psychopharmacology* 3, 125–129.

Steriade, M. & R.W. McCarley (1990). *Brainstem control of wakefulness and sleep*. New York: Plenum Press.

Strecker, R.E. et al. (2000). *Behavioural Brain Research* 115, 183–204.

Ticho, S.R. & M. Radulovacki (1991). *Pharmacology Biochemistry and Behavior* 40, 33–40.

von Economo, C. (1930). *Journal of Nervous and Mental Disorders* 71, 249–259.

Whyte, N.B. (1989). *International Journal of Eating Disorders* 9, 577–581.

Williams, R.L. et al. (1974). *Electroencephalography (EEG) of Human Sleep: Clinical Applications.* New York: John Wiley and Sons.

Wilson, S.J. et al. (1997). *The Lancet* 350, 185.

Wyatt, R.J. (1972). *Biological Psychiatry* 5, 33–64.

Dreaming

Cholinergic and dopaminergic hypotheses

Mark Solms

1. Introduction

Dreaming is a state of consciousness which has attracted considerable theoretical interest, perhaps mainly due to its phenomenological resemblance to some psychotic states.

About 25 years ago, the neurochemistry of dreaming seemed fairly well established. Following the discovery of rapid-eye-movement (REM) sleep by Aserinsky and Kleitman (1953; 1955), and its very high correlation with subjective reports of dreams (Dement & Kleitman, 1957a; 1957b), the conscious state of dreaming came to be widely equated with the physiological state of REM sleep. The precise extent of this correlation was and remains controversial. However, by conservative estimates, reports of vivid dreaming are elicited in approximately 70–95% of awakenings from REM sleep and approximately 5–10% of awakenings from non-REM (NREM) sleep (Nielsen, 1999). Since homologues of the human REM state are clearly recognisable in other mammalian species, the equation: REM = dreaming made it possible for basic neuroscientists to probe the neural mechanism of dreaming via animal models—notwithstanding the fact that the subjective experience of dreaming in animals is inaccessible to objective study.

2. The cholinergic (activation-synthesis) hypothesis

By 1962 the causal mechanism of REM/dreaming had been isolated to the pontine brainstem. The entire forebrain, diencephalon and midbrain were shown by Jouvet (1962) to be basically unnecessary for the maintenance of a normal

REM cycle. It is now generally accepted that the REM state can only be obliterated by substantial pontine lesions (Jones, 1979). Analogous observations have been made in human clinical cases (see Solms, 1997; 2000 for review).

By 1975 McCarley and Hobson had identified the specific nuclei within the pontine brainstem that control the REM cycle. The essential features of their reciprocal interaction model (McCarley & Hobson, 1975) are still widely accepted today. According to the latest version of this model (Hobson et al., 2000), 'REM-on' nuclei are primarily cholinergic and are located principally in the mesopontine tegmentum (pedunculopontine and lateral dorsal tegmentum, acting through the medial pontine reticular formation), while 'REM-off' nuclei are aminergic and are located principally in the (serotonergic) dorsal raphe and (noradrenergic) locus coeruleus complex. These two sets of nuclei are thought by McCarley and Hobson to have a reciprocal activating and inhibiting effect on each other.

This well-substantiated reciprocal interaction model of REM sleep control provided the physiological basis for Hobson and McCarley's (1977) more speculative activation-synthesis model of dreaming. According to the latter model, which was also generally accepted until very recently, the dream state is characterised (indeed caused) by cholinergic activation of the aminergically demodulated forebrain. On this model, the sleeping (aminergically demodulated) forebrain "makes the best of a bad job" (Hobson & McCarley, 1977, p. 1347) by attempting to synthesise from memory the meaningless images that are spontaneously generated by bottom-up cholinergic activation (hence the term: activation-synthesis).

3.   Problems of definition

The activation-synthesis model rests heavily on the equation REM = dreaming. The established neurochemistry of the REM state can explain the phenomenology of the dream state only to the extent that this equation is accepted. If dreams are shown to occur independently of the REM state, then the unique physiology of REM cannot account for the unique phenomenology of dreaming.

The equation REM = dreaming was first brought into question by the observation that reports of complex mentation can be elicited upon awakening from NREM sleep at a rate of approximately 50% (Foulkes, 1962). However, 'complex mentation' is not synonymous with 'dreaming'. It is generally recognised that NREM dreams are distinguishable from REM dreams

across a range of qualitative criteria (e.g., length, perceptual vivacity, emotional intensity, bizarreness, etc). In essence, the average NREM dream is certainly more "thoughtlike" than REM dreams (Nielsen, 1999). The fact therefore remains that only 5–10% of NREM dreams are "indistinguishable by any criterion"—i.e. by blind raters—from REM dreams (Hobson, 1988). In this way the equation REM = dreaming is preserved, so long as the term 'dreaming' is reserved for the distinctive type of mentation that characterizes the REM state significantly more frequently than it does the NREM state.

4.   Other problems with the cholinergic hypothesis

4.1 NREM dreaming

If it is accepted that 5–10% of NREM reports are "indistinguishable by any criterion" from REM reports, then this implies that roughly one-quarter of all REM-like dreams occur outside of REM sleep. Comparisons of the relative incidence of REM-like dream reports across the two states must take account of the fact that NREM sleep occupies 75%, and REM sleep only 25%, of our sleeping hours. Moreover, the 25% of REM-like dreams that occur during NREM sleep are not evenly distributed across the various NREM stages. The incidence of REM-like dreaming is almost negligible during NREM stage 4, for example, but it rises to approximately 70% at sleep onset (descending NREM stages 1 and 2). The incidence of NREM dreaming also increases exponentially in the late morning, with the rising morning phase of the diurnal rythym (Kondo et al., 1989). To the extent that sleep onset and late morning dreams (and to a lesser extent, nightmares) are not associated with cholinergic activation of an aminergically demodulated forebrain, the activation-synthesis model cannot be sustained.

Nielsen (2000) has recently attempted to preserve the equation REM = dreaming by suggesting that NREM dreams may be associated with dissociated (or 'covert') REM events. However this suggestion is entirely speculative (Solms, 2000a).

4.2 Effects of anticholinergic drugs and lesions

On to the activation-synthesis hypothesis, according to which dreams are caused by a cholinergically activated forebrain, anticholinergic medications and damage to cholinergic forebrain structures should produce decreased fre-

quency of dreaming and REM-like mentation. In fact, the opposite occurs. Cartwright (1966) was the first to observe that anticholinergic drugs (e.g., scopolamine, atropine) intensify dreaming and dreamlike mentation (see also Ketchum et al., 1973; see Perry & Perry, 1995 for review). Likewise, numerous authors have reported clinical cases in which structural damage to basal forebrain nuclei produce increased vividness and frequency of dreaming (see Solms, 1997 for review).

Also, it has never been demonstrated that structural damage to the pontine cholinergic nuclei, which are presumed to activate the dreaming forebrain during the REM state, produce a cessation of REM-like dreaming (see Solms, 2000b for review).

4.3   Ascending cholinergic pathways

It is difficult to reconcile these findings with the hypothesis that dreaming is characterised (or caused) by a cholinergically activated forebrain. In this connection, Braun (1999) has pointed out that it is not at all clear what role acetylcholine plays in the forebrain during REM sleep. Although the pedunculopontine (PPN) and lateral dorsal tegmentum (LDT) nuclei—which represent the major cholinergic output of the medial pontine reticular formation (mPRF)—are certainly highly active during REM, there is no evidence that all their ascending projections to the diencephalon and forebrain are themselves cholinergic (mPRF neurons clearly are not). Direct projections from brainstem cholinergic nuclei to the neocortex are rare; the principal targets of these nuclei are thalamus, basal forebrain, subcortical limbic structures, and other portions of the brainstem. But even if the effects on the forebrain were mediated by direct ascending projections of the PPN and LDT themselves, it still is not clear that the most critical synapses are cholinergic. Noncholinergic cells projecting from these nuclei innervate as widespread an array of targets within the forebrain as do their cholinergic counterparts. And while single unit studies show that these nuclei are active during REM, it is unknown whether the active cells are cholinergic, and whether they project to the cortex. There is even some evidence for the view (Solms 1999) that ascending pontine cholinergic projections actively inhibit cholinergic forebrain sites during REM sleep: LDT projections, at least, to the basal forebrain synapse on noncholinergic neurons which may be inhibitory internuncials (Rye, personal communication to Braun cited in (Braun, 1999)).

5.   An alternative, dopaminergic hypothesis

Solms (2000b) recently suggested that dreaming and REM sleep are controlled by different brain mechanisms. This hypothesis rests on the observation that dreaming and REM sleep are doubly dissociable states. That is, dreams can occur without REM, and REM can occur without dreams—under both normal and pathological conditions. Some of the evidence for this conclusion has been reviewed above. Roughly one-quarter of REM-like dreams occur during NREM sleep. This figure rises substantially during specific NREM epochs, e.g., at sleep onset, where it approaches REM levels (long before the first REM period occurs). Likewise, not all REM awakenings are productive of dream reports. This is especially apparent in pathological cases, where cessation of dreaming is associated with lesions in specific forebrain structures which completely spare the REM state (Solms, 1997). Conversely, lesions which obliterate REM (or REM-generating structures in the pontine brainstem) have not been shown to obliterate dreaming (Solms, 2000b). Also, complex partial seizures during NREM sleep (which are focal forebrain events by definition) cause distinctive nightmare phenomena which certainly cannot be attributed to pontine brainstem REM mechanisms (see Solms, 1997 for review).

If REM and dreaming are dissociable, two questions arise: (1) what is the mechanism of dreaming per se? (2) why is this mechanism typically (albeit not necessarily) co-activated with REM?

An obvious source of evidence for the first question is the clinical literature in which lesions obliterate dreaming but spare REM sleep (Solms, 1997). Cessation of dreaming in such cases is associated with two lesion sites: the region of the parieto-temporo-occipital (PTO) junction of either hemisphere, and the ventromesial frontal region of both hemispheres. The former site is less enlightening than the latter with respect to the causal mechanisms of dreaming. The PTO junction is well known to subserve visuospatial perception and cognition in general, and mental imagery in particular (Kosslyn, 1994). The fact that lesions here obliterate dreaming is easily reconciled with the activation-synthesis model: cholinergic brainstem activation is preserved but forebrain synthesis (dream representation) is impaired.

It is more difficult to account for the frequently reported fact that bilateral damage to the white matter immediately inferior to the frontal horns of the lateral ventricles obliterates dreaming (see Solms, 1997 for review).

Many fibre systems course through this region of the brain. It is therefore difficult to determine which aspect of the lesion produces the observed cessation of dreaming. Converging lines of evidence suggest that the critical

component of the lesion is the ascending dopaminergic pathway (the mesocortical/mesolimbic dopamine system) coursing from the ventral tegmental area (VTA), via the lateral hypothalamus, to the nucleus accumbens of the ventral striatum and other forebrain structures (prefrontal cortex, anterior cingulate gyrus, amygdala). The first line of evidence is that surgical sectioning of this pathway (by modified prefrontal leucotomy) produces cessation of dreaming together with amelioration of the positive symptoms of schizophrenia, which bear a close resemblance to dream mentation (e.g. delusions, hallucinations; reviewed, Solms, 1997, see also Chapter 8). Post-surgical preservation of dreaming was even considered a poor prognostic sign in the days of prefrontal leucotomy (Piehler, 1950). The analogy with the dopamine hypothesis of schizophrenia is readily apparent. The second line of evidence is that cessation of dreaming, like prefrontal leucotomy, is associated with decreased motivation (Solms, 1997); and decreased motivation is also a well-established consequence of damage to mesocortical/mesolimbic dopamine pathways (Panksepp, 1985; see Chapter 5). The third line of evidence is that dreaming and dreamlike mentation is intensified by drugs which stimulate these pathways (such as L-Dopa (Nausieda et al., 1982, Scharf et al., 1978). Of particular interest in this regard is the observation that dreaming is acutely intensified, across a number of 'REM-like' parameters (e.g. emotional intensity, bizareness, length) by the administration of L-Dopa in normal subjects, and that these effects occur independently of any concomitant effects on the REM state (Hartmann et al., 1980). When assessing the effects of medications on dreaming, care must always be taken to distinguish dream effects from REM effects. This is especially important if one accepts that the mechanisms of dreaming and REM sleep interact in some important way.

6.   Problems with the dopaminergic hypothesis

If dreaming is indeed stimulated by a mesocortical/mesolimbic DA mechanism, and not by the pontine cholinergic mechanism that triggers REM sleep, the question remains as to why dreaming and REM sleep should co-occur with such regularity?

One obvious answer is to suggest that the state of activation that characterises the REM state (replete with genital engorgement) attracts the appetitive interest of the organism, and thereby secondarily activates the well-established motivational mechanisms subserved by mesocortical/mesolimbic dopaminergic circuits (the 'seeking system' of Panksepp, 1998; see also Chapter 5). How-

ever, if this were the case, one might expect to find that REM sleep triggers bursts of activity in VTA dopaminergic neurons. This has never been demonstrated. What is observed, instead—at least in rats and cats—is that these neurons (in contrast to their serotonergic and noradrenergic counterparts, which decrease dramatically at sleep onset, and even more so with the onset of REM) continue firing at their usual, high regular rate throughout sleep (Miller et al., 1983, Trulson & Preussler, 1984). However, further research on this issue is necessary. There are substantial differences in forebrain VTA dopaminergic innervation in rats, cats and primates (Berger et al., 1991); and it is difficult to interpret the observation that rat VTA dopaminergic cells fire with a more variable interspike interval during REM than NREM sleep (Miller et al., 1983).

7. Possible interactions between dopamine and other neurotransmitters

Another way of conceptualising the relationship between dreaming and REM sleep is to suggest, with Braun (1999), Gottesmann (2000) and Perry and Piggott (2000), that the mesocortical/mesolimbic dopaminergic systems implicated in dream generation by the lesion and pharmacological evidence reviewed above, are but one factor in a dynamic formula which also incorporates cholinergic, serotonergic and noradrenergic systems. For example, dreaming might be attributed to forebrain activation (whether this activation is caused by cholinergic REM or other, NREM arousal mechanisms is immaterial) plus mesocortical/mesolimbic dopaminergic activation minus neocortical noradrenergic and serotonergic modulation. From the psychological viewpoint, this might imply that dreaming is a nonspecific state of activation characterised by relatively increased motivational salience coupled with relatively decreased cognitive control. Such a formulation would certainly be consistent with the emerging functional imaging evidence, which suggests that the dreaming brain (like the acutely schizophrenic brain, Silbersweig et al., 1995) is characterised by massively increased limbic forebrain activation coupled with dorsolateral prefrontal hypoactivation (Braun et al., 1997). A multi-factorial model of this kind, in which dreaming is conceptualised in relation to the relative balance between a number of neuromodulators, seems particularly apt to account for the varieties of dreaming that certainly occur in nature.

8. Conclusion

Although a central role for dopamine has yet to be acknowledged by the authors of the original activation-synthesis model, a more flexible, dynamic formula of this kind is included in the latest revisions of their model, now styled the AIM (activation-input-mode) model (Hobson et al., 2000). This increasing understanding of the neurochemistry of dreaming promises to shed important new light on the neurochemistry of consciousness in general, and endogenously generated conscious states (e.g., hallucinations, delusions) in particular.

References

Aserinsky, E. & N. Kleitman (1953). *Science* 118, 273–274.

Aserinsky, E. & N. Kleitman (1955). *Journal of Applied Physiology* 8, 1–10.

Braun, A. (1999). *Neuro-Psychoanalysis* 1, 196–201.

Braun, A. et al. (1997). *Brain* 120, 1173–1197.

Cartwright, R. (1966). *Archives of General Psychiatry* 15, 7–15.

Dement, W. & N. Kleitman (1957a). *Electroencephalography & Clinical Neurophysiology* 9, 673–690.

Dement, W. & N. Kleitman (1957b). *Journal of Experimental Psychology* 53, 543–553.

Foulkes, D. (1962). *Journal of Abnormal & Social Psychology* 65, 14–25.

Gottesmann, C. (2000). *Behavioral & Brain Sciences* 23, 940–942.

Hartmann, E. et al. (1980). *Sleep Research* 9, 153.

Hobson, J.A. (1988). *The Dreaming Brain*. New York: Basic Books.

Hobson, J.A. & R. McCarley (1977). *American Journal of Psychiatry* 134, 1335–1348.

Hobson, J.A. et al. (2000). *Behavioral & Brain Sciences* 23, 793–842.

Jones, B. (1979). *Neuroscience Letters* 13, 285–293.

Jouvet, M. (1962). *Archives Italiennes de Biologie* 100, 125–206.

Ketchum, J. et al. (1973). *Psychopharmacologia* 28, 121–145.

Kondo, T. et al. (1989). *Sleep Research* 18, 147.

Kosslyn, S. (1994). *Image and Brain.* Cambridge MA, MIT.

McCarley, R. & J.A. Hobson (1975). *Science* 189, 58–60.

Miller, J. et al. (1983). *Brain Research* 273, 133–141.

Nausieda, P. et al (1982). *Clinical Neuropharmacology* 5, 183–194.

Nielsen, T. (1999). In R. Lydic & H. Baghdoyan (Eds.), *Handbook of Behavioural State Control* (101–128). Boca Raton FL: CRC Press.

Nielsen, T. (2000). *Behavioral & Brain Sciences* 23, 851–866.

Panksepp, J. (1985). In P. Vinken et al. (Eds.), *Handbook of Clinical Neurology* 45 (271–285). Amsterdam: Elsevier.

Panksepp, J. (1998). *Affective Neuroscience.* New York: Oxford University Press.

Perry, E. & R. Perry (1995). *Brain & Cognition* 28, 240–258.

Perry, E. & M. Piggott (2000). *Behavioral & Brain Sciences* 23, 990–991.

Piehler, R. (1950). *Nervenaerzt* 21, 517–521.

Scharf, B. et al. (1978). *Journal of Neural Transmission* 43, 143–151.

Silbersweig, D. et al. (1995). *Science* 378, 176–179.

Solms, M. (1997). *The Neuropsychology of Dreams*. Mahwah NJ: LEA.

Solms, M. (1999). *Neuro-Psychoanalysis* 1, 183–195.

Solms, M. (2000a). *Behavioral & Brain Sciences* 23, 1008–1009.

Solms, M. (2000b). *Behavioral & Brain Sciences* 23, 843–850.

Trulson, M. & D. Preussler (1984). *Experimental Neurology* 83, 367–377.

Dreaming

Monoaminergic disinhibition hypothesis

Claude Gottesmann

1. Introduction

The study of dreaming was long the exclusive territory of humanities which described this particular mode of mentation and tried to find its innate significance, most often by symbolic interpretation. With Freud (1900) this approach blossomed although already in the Talmud it is written "an uninterpreted dream is an unread letter" (Fromm, 1953).

Nearly fifty years ago Aserinski and Kleitman (1953) described the close association between rapid eye movement sleep (REM sleep) and dreaming in man. Later work (Jouvet et al., 1960), using electrical brainstem stimulation in cats, identified some of the structures involved in this similar stage of sleep in animals and also suggested that neurochemical transmission was involved. The same year Jouvet and Michel (1960) showed that atropine, a muscarinic receptor antagonist, and chlorpromazine, a broad spectrum dopamine receptor antagonist, suppressed REM sleep in cats, while the anticholinesterases prostigmine and eserine increased it. The first step towards deciphering the neurochemistry of REM sleep, and possibly of dreaming in man, had been taken. Since then major progress has been made in the characterisation of this sleep stage, in the unveiling of the central structures responsible for its generation, and in the determination of its neurochemical support.

2. Characterisation of rapid eye movement sleep (REM sleep)

The first identified pattern was the rapid eye movements which occur periodically during sleep in man (Aserinski & Kleitman, 1953), giving rise to the
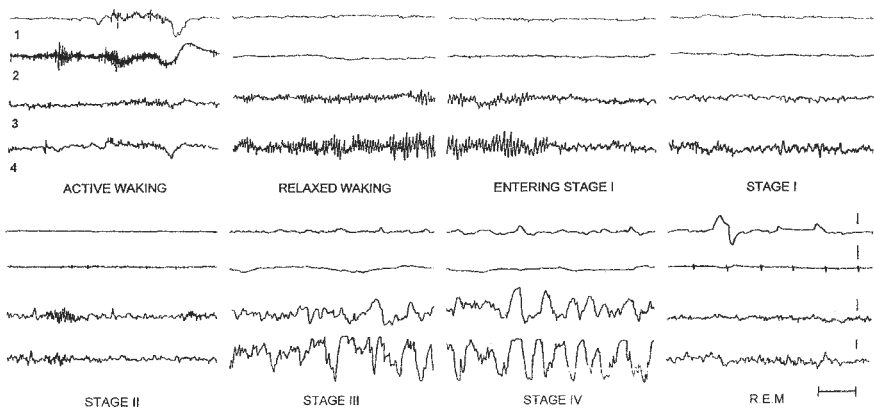
Figure 1. Sleep-waking stages in humans. The subject was first recorded during active waking with low voltage electroencephalographic (EEG) activity and strong muscular (EMG) activity at masseter level. During quiet waking alpha rhythm appears, principally at posterior level. When falling asleep, the alpha rhythm disappears and low voltage EEG activity occurs which is characteristic of Stage I, during which hypnagogic hallucinations occur. Recent data show that, in some cases, short dreams sometimes associated with slow eye movements (Nielsen, 2000). Stage II is characterized by spindles and K complexes. During Stage III, slow and high amplitude delta waves occupy up to 50% of recording time, and are almost permanent during Stage IV. During these stages of "slow wave sleep" abstract, theoretical "thought-like mental activity" is reported by subjects on awakening. Rapid eye movement sleep (REM sleep) is characterized by low voltage EEG, rapid eye movements and abolition of muscular tonus. Only an electrocardiogram artefact can be seen on the silent EMG lead. REM sleep is the principal stage of dreaming.
Abbreviations: 1 Eye movements 50 μV, 2 EMG 12.5 μV, 3 Frontal (Fz) cortex 50 μV, 4 Parietal (Pz) cortex 50 μV. Time scale 1 sec. (From P. Gauthier and C. Gottesmann, unpublished).

term rapid eye movement sleep (REM sleep), or paradoxical sleep in animals (Jouvet et al., 1959; Jouvet, 1965). Aserinski and Kleitman (1953) also observed cortical rapid low voltage electroencephalographic (EEG) activity during REM sleep which contrasted with the slow, high amplitude cortical waves present in deep sleep (slow wave sleep, SWS; Fig. 1). This EEG criterion of REM sleep and dreaming in man was definitively established by Dement and Kleitman (1957a,b), while similar EEG activity led Dement (1958) to term this stage "activated sleep" in cats. At the peripheral level, postural atonia also characterised REM sleep in animals (Jouvet & Michel, 1959) and in man (Berger, 1961).

However, since consciousness principally involves the cerebral cortex, it is important to obtain information about its functional state during REM sleep. Evarts (1962) observed in the monkey that neurons in the visual cortex fired more strongly during REM sleep than during SWS, while Arduni et al. (1963) and Evarts (1964) showed that cortical pyramidal neurons in the cat also fired more intensely during REM sleep (Fig. 2). In these two studies the firing rates were found to be similar in REM sleep and active waking. Alongside this tonic cortical activation in REM sleep, there were phasic increases in cortical excitability associated with ponto-geniculo-occipital (PGO) waves in cats (Jouvet & Michel, 1959; Mikiten et al., 1961; Michel et al., 1964; Satoh, 1971;) and in humans (McCarley et al., 1983; Fig. 3).

Recently it has been observed that, as during waking, a synchronised gamma rhythm centred on 40Hz is more evident during REM sleep than during SWS. This activity is thought to be associated with cognitive function and its amplitude is markedly decreased in Alzheimer's disease (Llinas & Ribary, 1993; Gross & Gotman, 1999; Chapter 14; Fig. 4). In addition, positron emission tomography has shown that cerebral blood flow, another indirect criterion of brain activation, is increased in REM sleep compared with SWS, particularly in phylogenetically older limbic cortical areas. Cerebral blood flow is even greater during REM sleep that during waking (Madsen et al., 1991; Maquet et al., 1996; Maquet, 2000; Braun et al., 1997, 1998) except in some dorsolateral prefrontal and parietal cortex areas (Fig. 5). In view of all these observations that the brain is highly active during REM sleep, it is not surprising that it is able to generate mentation in the form of dreams.

Nevertheless, the brain is never silent psychologically. At sleep onset, when there is normally no REM sleep, hypnagogic hallucinations can occur, and Foulkes (1962) identified thought-like mentation and some dreaming during non-REM sleep. However, recent data shows that true dreaming with its specific visual and emotional qualities seems only to occur during REM sleep (Gottesmann, 1999; Takeuchi et al., 1999, 2001; Hobson, 2000; Nielsen, 2000).

3.   Neurochemistry of REM sleep

The rapid, low amplitude EEG activity of REM sleep, like that of waking, is sustained by cholinergic processes (Kinai & Szerb, 1965; Phillis & Chong, 1965), principally from neurons in the basal forebrain which project over the entire cortex (Divac, 1975; Lehmann et al., 1980; Bigl et al., 1982). Activation of the nucleus basalis of Meynert results in acetylcholine release in the cortex

VISUAL CORTEX NEURONS

PYRAMIDAL NEURON
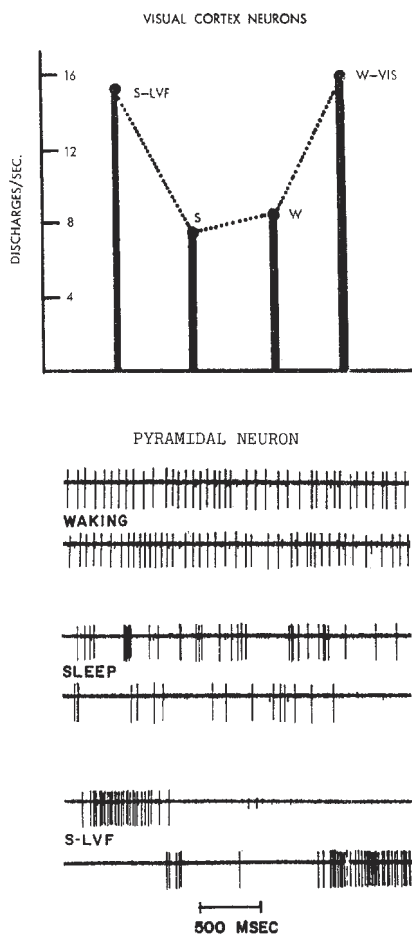
Figure 2. Evarts (1964, 1965) recorded neuron unicellular activity in the visual cortex of cats (top) and in the motor cortex of monkeys (bottom). In both cases, the neuron activity was much more marked during REM sleep than during slow wave sleep. In many cases the firing rate was as high as during active waking. Interestingly, for the high irregular activity of pyramidal neurons during REM sleep, Evarts (1964) stated "it is suggested that the occurrence of high-frequency bursts during slow wave sleep and REM sleep may result from a reduction in the effectiveness of some frequency-limiting mechanism which acts to stabilize discharge during waking" (p. 170). It was the first time that suppression of a cortical control during sleep, based on electrophysiological data, was mentioned.

Abbreviations: S-LVF REM sleep; S slow wave sleep; W quiet waking; W-vis waking with visual exploring. From Editions du CNRS. 1965 (top) and Journal of Neurophysiology, 1964 (bottom) with permission.
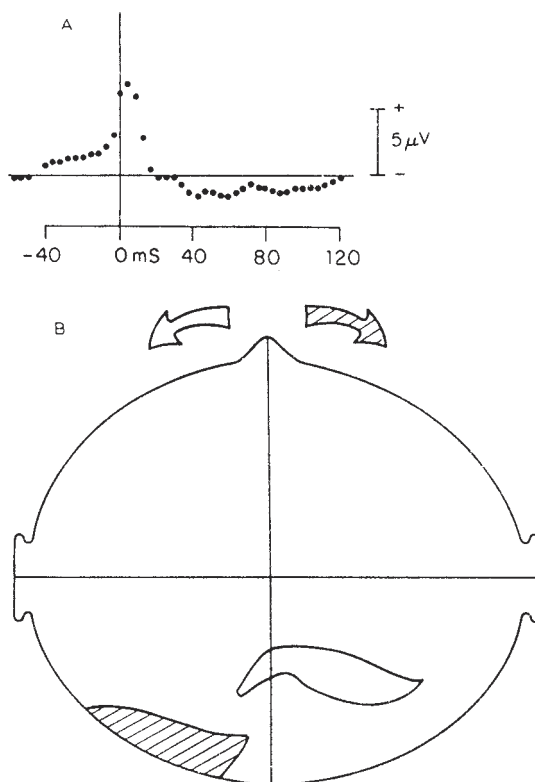
Figure 3. McCarley et al. (1993) recorded during human REM sleep, cortical phasic waves equivalent of cat ponto-geniculo-occipital (PGO) waves. The spikes began shortly prior to the eye movements (top). The spikes related to right directed eye movements were recorded on the left cortex (hatched) and left directed eye movements were associated with right situated spikes (open). From Elsevier, with permission.

as shown by Kurosawa et al. (1989) in rats, and spontaneous release is slightly higher during REM sleep than during waking, and much higher than during SWS in cats (Jasper & Tessier, 1971; Marrosu et al., 1995). Released acetylcholine partly acts on cortical muscarinic receptors, since atropine suppresses cortical waking activation and induces slow high amplitude waves characteristic of SWS in dogs (Wikler, 1952). Brainstem structures, particularly mesopontine, are responsible for the basal forebrain activation, and for all characteristics of REM sleep. Indeed, the neurons of the peri-locus coeruleus-α (Sakai, 1988; Onoe & Sakai, 1995) and some cells from the cholinergic pedunculo-pontine and dorso lateral tegmental nuclei (Steriade & McCarley, 1990) become active
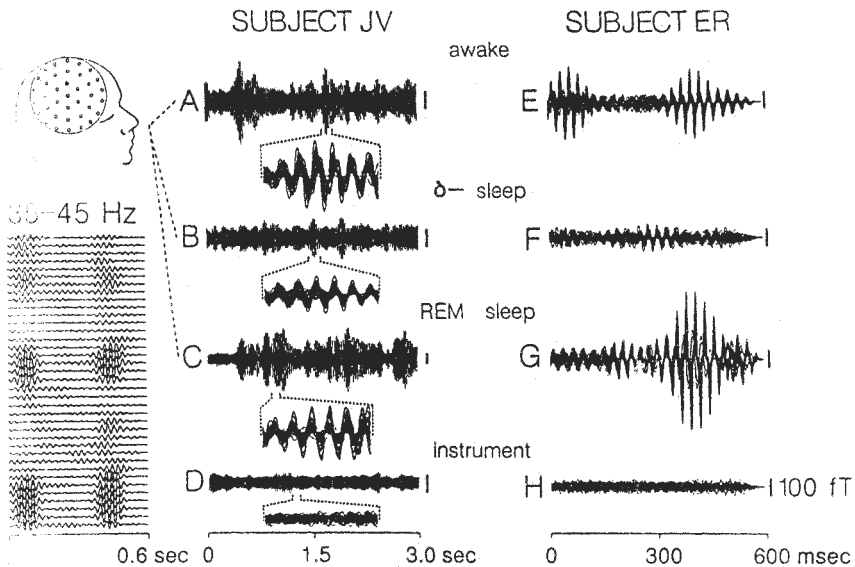
Figure 4. Llinas and Ribary (1993) identified in humans a synchronized gamma rhythm centred on 40 c/s during waking and sleep. In the two subjects (JV and ER), it was much more present during waking (A) and REM sleep (C) than during slow wave sleep (B, δ sleep). D shows the noise of the system. Thirty-seven superimposed traces. Reprinted from Proceedings of National Academy of Science, with permission.

during REM sleep and influence the rostral structures including the Meynert nucleus. The phasic PGO waves are also influenced by cholinergic neurons located in these brainstem nuclei (Koyama & Sakai, 2000).

In parallel with this cortical activation which occurs similarly during waking and REM sleep, and is markedly decreased during SWS, inhibitory influences are altered in the cortex during sleep-waking stages. Dopaminergic (Fuxe et al., 1974), noradrenergic (Fuxe et al., 1968) and serotonergic (Fuxe, 1965) neurons located in the brainstem and histaminergic neurons (Schwartz, 1975) in the hypothalamus all innervate the cortex. They have predominantly inhibitory influences on cortical inhibitory neurons, either directly or by activating cortical inhibitory neurons (Krnjevic & Phillis, 1963; Frederickson et al., 1971; Nelson et al., 1973; Sastry & Phillis, 1976; Fig. 6). Noradrenergic, serotonergic and histaminergic neurons are active during waking, decrease their firing rate during SWS (histaminergic neurons become silent from sleep onset (Vanni-Mercier et al., 1984)), and become silent or nearly silent just before and during REM sleep (Hobson et al., 1975; McGinty & Harper, 1976; Aston-Jones
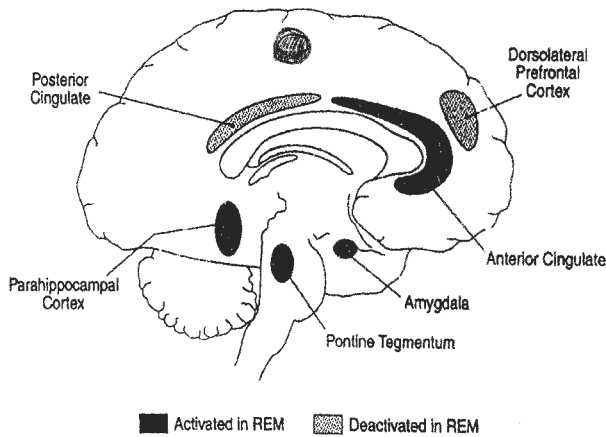
Figure 5. Positron emission tomography shows the brain areas activated and deactivated during REM sleep when compared to waking. In the forebrain, more activated areas are principally limbic structures, while the posterior cingulate cortex, part of the prefrontal and parietal cortex, are deactivated. Modified from Hobson et al. (1998). Reprinted from NeuroReport with permission.

& Bloom, 1981; Fig. 7). Only the dopaminergic neurons fire without significant changes during all sleep-waking stages (Miller et al., 1983; Trulson & Preussler, 1984; Fig. 8).

Consequently, during waking the cortex is under both strong activating and inhibitory influences; during SWS there is a decrease of both, while during REM sleep the cortex is strongly activated but also largely disinhibited. This divergent pattern of activation indicates differential properties for mentation occurring during the various sleep stages.

4. Correlation between brain neurochemical state and dreaming mentation

All the electrophysiological, circulatory and neurochemical evidence shows that the cortex is as strongly activated tonically in REM sleep as in waking. Thus this most recent phylogenetic structure is able to function and would be able to generate dreaming mentation. The phasic PGO wave activation has long been supposed to be responsible for inducing the imagery of dreaming (McCarley et al., 1983; Callaway et al., 1987). However, these spikes exert only short-lasting effects of about 100 msec in humans (McCarley et al., 1983; Miyauchi
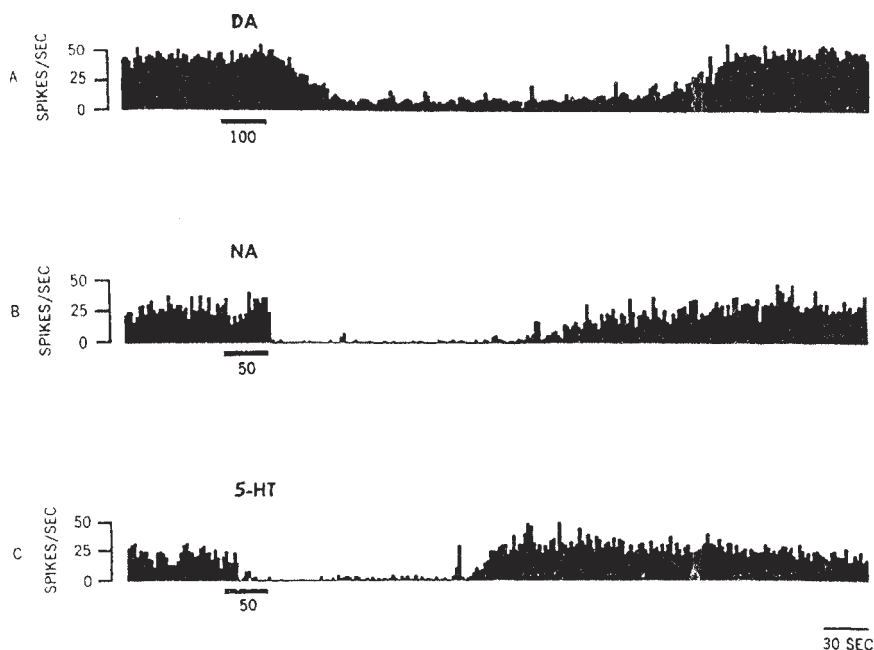
Figure 6. Reader et al. (1979) showed that microiontophoretic application of dopamine (DA), noradrenaline (NA) and serotonin (5-HT) inhibits cortical neurons activated by acetylcholine. Reprinted from Elsevier, with permission.

et al., 1987). Dreams appear to have a different time scale, unless it is accepted that successive spikes might be responsible for rapid changes in dream content (Gottesmann, 2000).

Acetylcholine is mainly involved in cortical tonic activation and related mentation (Perry et al., 1999; Sarter & Bruno, 2000). However, during waking monoaminergic inhibitory influences are likely also to be involved in this more complex cerebral functioning, and could exert a control over cholinergic activation (Gottesmann, 1999). It can be hypothesised that both kinds of influences cooperate to generate the logical, rational mentation of waking. During REM sleep, in spite of powerful cortical activation allowing mentation, the postulated cooperation and control exerted by noradrenaline and serotonin is suppressed. This could explain the characteristic illogical and irrational associations and the telescoping of contents of successive dreams contents that occur in REM sleep dreaming. This unusual brain functioning could also explain the frequent unpleasant repetitive dreams of dramatic events: specific memory traces with important emotional load may repeatedly enter the consciousness
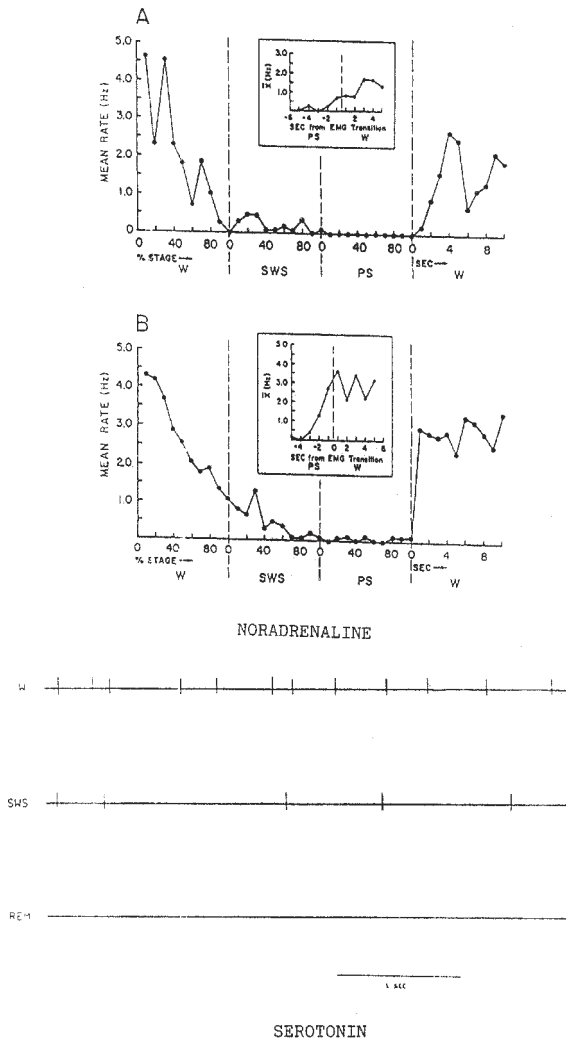
Figure 7. *Top.* Aston-Jones and Bloom (1981) showed in rats (by single (A) and multiunit (B) recordings) that the noradrenergic neurons in the locus coeruleus fire maximally during waking (w), decrease their firing rate during slow wave sleep (sws) and become silent during REM sleep (ps). As shown in the insets these neurons anticipate the reappearance of dorsal neck muscle activity during waking. Reprinted from Journal of Neurosience, with permission.
Bottom. McGinty and Harper (1976) similarly recorded the dorsal raphe nucleus in cats. Here also, maximal firing occurred during waking, there was a decrease during slow wave sleep, and the neurons became silent during REM sleep. Reprinted from Elsevier, with permission.
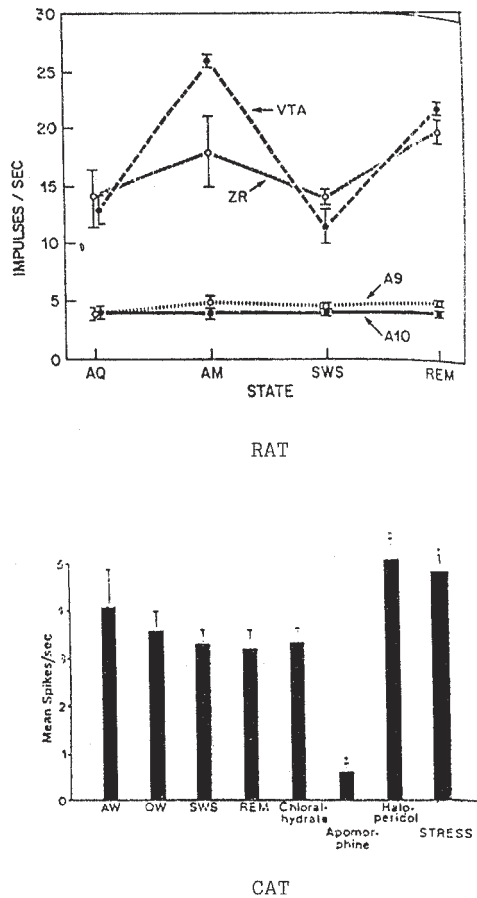
Figure 8. *Top*. Miller et al. (1983) showed in rats that the neurons in areas 9 (substantia nigra) and 10 (ventral tegmental area at the origin of the mesolimbic and mesocortical projections) fire similarly during all sleep-waking stages (lower curves).

Abbreviations: VTA ventral tegmental area; ZR zona reticulata of substantia nigra; AQ quiet waking; AM moving waking; SWS slow wave sleep. Reprinted from Elsevier, with permission.

Bottom. Trulson and Preussler (1984) confirmed in cats the similar mode of firing of area 10 neurons during waking and natural sleep. *Significantly different from quiet waking control, P > 0.05.

Abbreviations: AW active waking, QW quiet waking. Reprinted from Experimental Neurology, with permission.

of the dreamer by a lowering of recall threshold due to disinhibition. Difficulty in recalling dreams, and the tendency to forget them shortly after awakening may be due to the reappearance of noradrenergic, histaminergic and perhaps serotonergic influences which shortly anticipate arousal from REM sleep and abruptly change the brain state (Aston-Jones & Bloom, 1981; see inserts Fig. 7).

A major feature of neurochemistry of sleep is that dopaminergic neurons fire similarly throughout the sleep-wake cycle. Dreaming consciousness comprises a unique type of mentation characterised by "sensorimotor hallucinations, bizarre imagery ... diminished self-reflexive awareness, orientational instability ... intensification of emotion, instinctual behaviours" (Hobson et al., 1998), symptoms generally encountered in schizophrenia. Nightmares are induced by dopamine agonists (Thompson & Pierce, 1999), and excessive dopamine release by amphetamine (Pehek, 1999) leads to psychotic disorders (Buffenstein et al., 1999). Moreover, neuroleptics used to alleviate schizophrenia reduce dopamine activity by an action at the pre and/or post synaptic level (Kinon & Liberman, 1996). Nevertheless, dopamine alone cannot explain the psychotic-like mental functioning of dreaming, because of the identical firing of dopaminergic neurons during waking without such pathological mentation. The silence of noradrenergic neurons during REM sleep could, however, exaggerate the cortical dopaminergic influence. Indeed, α_{2a} receptors situated on axon terminals of cortical dopaminergic neurons (Gobert et al., 1998), which inhibit dopamine release when activated, become inactive during REM sleep. Similarly, post-synaptic noradrenergic α_1 receptors which decrease dopamine activation of D_1 receptors (Gionni et al., 1998) become silent during REM sleep. These concerted actions could result in an excess of dopaminergic influence which would reach the threshold at which psychotic disturbances become manifest during waking. In favour of this conclusion is the observation that new atypical neuroleptics increase adrenaline release in the cortex (Nutt et al., 1997).

Evidence concerning the effect of serotonin on cortical functioning is still ambiguous. Cortical disinhibition linked to the silence of serotonergic neurons seems to be accompanied by decreased dopamine release due to suppression of an action on post-synaptic $5\text{-}HT_{1A}$ receptors, the precise location of which has not been identified (Sakaue et al., 2000). Inactivation of $5\text{-}HT_{1B}$ and $5\text{-}HT_6$ receptors, which stimulate dopamine release (Matsumoto et al., 1999), also occurs during REM sleep. This inhibitory influence of serotonin on dopamine release could be partly mediated by cortical interneurons. However, inactivation of $5\text{-}HT_6$ receptors by specific antagonists does not alter dopamine release (Dawson et al., 2000) but leads to behavioural abnormalities in animals (yawn-

ing, stretching, chewing) which are reversed by atropine (Bourson et al., 1995), accompanied by increases in cortical glutamate, aspartate and acetylcholine concentrations in the striatum (Bourson et al., 1998). These excitatory transmitters are co-responsible for the cortical activation of REM sleep, and acetylcholine increases dopamine release by an action on nicotinic receptors (Nisell et al., 1996; Drew et al., 2000). It has recently been shown that 5-HT$_{1B}$ receptor knock-out mice show increased dopamine release in the nucleus accumbens (Shippenberg et al., 2000), a structure involved in schizophrenia (Boulenguez et al., 2000; Joseph et al., 2000). Increased dopaminergic activity in this nucleus may possibly account for the psychotic-like content of REM sleep dreaming.

5.   Conclusion

Experimental and clinical evidence concerning the neurochemical state of the cortex during REM sleep suggests that the mentation of dreaming in this sleep stage can be characterised by the equation (Gottesmann, 2000):

activation (acetylcholine), + disinhibition (suppression of inhibitory influence of noradrenaline, serotonin, histamine), + excessive dopaminergic influence.

Solms (2000; see also Chapter 7) has observed that suppression of cortical dopaminergic afferents abolishes dreaming. Dopamine therefore appears to be a neurotransmitter keystone of the common features of REM sleep, dreaming and schizophrenia.

References

Arduini, A. et al. (1963). *Archives Italiennes de Biologie* 10, 530–544.
Aserinski, E. & N. Kleitmann (1953). *Science* 118, 273–274.
Aston-Jones, G. & F.E. Bloom (1981). *Journal of Neuroscience* 1, 876–886.
Berger, R. (1961). *Science* 137, 601.
Bigl, V. et al. (1982). *Brain Research Bulletin* 8, 727–749.
Boulonguez, P. et al. (1998). *Journal of Psychopharmacology* 12, 258–267.
Bourson, A. et al. (1995). *Journal of Pharmacology and Experimental Therapeutics* 274, 173–180.
Bourson, A. et al. (1998). *British Journal of Pharmacology* 125, 1562–1566.
Braun, A. et al. (1997). *Brain* 120, 1173–1197.
Braun, A. et al. (1998). *Science* 279, 91–95.
Buffenstein, A. et al. (1999). *American Journal of Psychiatry* 156, 662.

Callaway, C.W. et al. (1987). *Cellular and Molecular Neurobiology* 7, 105–147.

Dawson, L.A. et al. (2000). *British Journal of Pharmacology* 130, 23–26.

Dement, W. (1958). *Electroencephalography and Clinical Neurophysiology* 10, 291–296.

Dement, W. & N. Kleitman (1957a). *Journal of Experimental Psychology* 53, 339–346.

Dement, W. & N. Kleitman (1957b). *Electroencephalography and Clinical Neurophysiology* 9, 673–690.

Divac, I. (1975). *Brain Research* 93, 385–398.

Drew, A. et al. (2000). *Synapse* 38, 10–16.

Evarts, E. (1962). *Journal of Neurophysiology* 25, 812–815.

Evarts, E. (1964). *Journal of Neurophysiology* 27, 152–171.

Evarts, E. (1965). In *Aspects anatomo-fonctionnels de la physiologie du sommeil* (189–212). Paris: CNRS

Foulkes, D. (1962). *Journal of Abnormal Social Psychology* 65, 14–25.

Frederickson, R.C.A. et al. (1971). *Brain Research* 35, 556–560.

Freud, S. (1900). *The Traumdeutung*. Standard Edition, Vol. IV. London: The Hogarth Press, vol. XII. London: The Hogarth Press.

Fromm, E. (1953). *Le Lngage oublie*. Paris, Payot.

Fuxe, K. (1965). *Acta Physiologica Scandinavica, 64* (suppl. 247), 37–84.

Fuxe, K. et al. (1968). *Brain Research* 8, 125–131.

Fuxe, K. et al. (1974). *Brain Research* 82, 349–355.

Gioanni, Y. et al. (1998). *Synapse* 30, 362–370.

Gobert, A. et al. (1998). *Neuroscience* 84, 413–429.

Gottesmann, C. (1999). *Progress in Neurobiology* 59, 469–508.

Gottesmann, C. (2000). *Behavioral and Brain Sciences* 23, 940–942.

Gross, D.W. & J. Gotman (1999). *Neuroscience* 94, 1005–1018.

Hobson, A. et al. (1995). *Science* 189, 55–58.

Hobson, A. et al. (1998). *NeuroReport* 9, R1–R14.

Hobson, A. et al. (2000). *Behavioral Brain Sciences* 23, 793–842.

Jasper, H.H. & J. Tissier (1971). *Science* 172, 601–602.

Jouvet, M. (1965). *Progress in Brain Research* 18, 20–62.

Joseph, M.H. et al. (2000). *Neuroscience* 101, 921–930.

Jouvet, M. & F. Michel (1959). *Comptes Rendus de la Societe de Biologie* 153, 422–425.

Jouvet, M. & F. Michel (1960). *Journal de Physiologie, Paris* 52, 130–131.

Jouvet, M. et al. (1959). *Comptes Rendus de l'Academie des Sciences* 248, 3043–3045.

Jouvet, M. et al. (1960). *Revue Neurologique* 103, 189–205.

Kinai, T. & J.C. Szerb (1965). *Nature* 205, 80–82.

Kinon, B. J. & J.A. Lieberman (1996). *Psychopharmacology* 124, 2–34.

Koyama, Y. & K. Sakai (2000). *Neuroscience* 96, 723–733.

Krnjevic, K. & J.W. Phillis (1963). *British Journal of Pharmacology* 20, 471–490.

Kurosawa, M. et al. (1989). *Neuroscience Letters* 98, 45–50.

Lehmann, J. et al. (1980). *Neuroscience* 5, 1161–1174.

Llinas, R. & U. Ribary (1993). *Proceedings of the National Academy of Sciences* 90, 2078–2080.

Madsen, P.L. et al. (1991). *Journal of Cerebral Blood Flow and Metabolism* 11, 502–507.

Maquet, P. (2000). *Journal of Sleep Research* 9, 207–231.

Maquet, P. et al. (1996). *Nature* 383, 163–166.

Marrosu, F. et al. (1995). *Brain Research* 671, 329–332.

Matsumoto, M. et al. (1999). *European Journal of Pharmacology* 383, 39–48.

McCarley, R.W. et al. (1983). *Brain Research* 274, 359–364.

McGinty, D.J. & R.M. Harper (1976). 101, 569–575.

Michel, F. et al. (1964). *Comptes rendus de la societe de Biologie* 158, 103–106.

Mikiten, T.M. et al. (1961). *Federation Proceedings* 20, 327.

Miller, J.D. et al. (1983). *Brain Research* 173, 133–141.

Miyauchi, S. et al. (1987). *Electroencephalography and Clinical Neurophysiology* 66, 383–390.

Nelson, C.N. et al. (1973). *Brain Research* 62, 115–133.

Nielsen, T. (2000). *Behavioral and Brain Sciences* 23, 851–866.

Nisell, M. et al. (1996). *Synapse* 22, 369–381.

Nutt, D.J. et al. (1997). *Journal of Psychopharmacology* 11, 163–168.

Onoe, H. & K. Sakai (1995). *NeuroReport* 6, 353–356.

Pehek, E.A. (1999). *Journal of Pharmacology and Experimental Therapeutics* 289, 273–280.

Perry, E. et al. (1999). *Trends in Neuroscience* 22, 273–280.

Phillis, J.W. & G.C. Chong (1965). *Nature* 207, 1253–1255.

Sakai, K. (1988). *Archives Italiennes de Biologie* 126, 239–257.

Sakaue, M. et al. (2000). *British Journal of Pharmacology* 129, 1028–1034.

Sarter, M. & J.P. Bruno (2000). *Neuroscience* 95, 933–952.

Sastry, B.S.R. & J.W. Phillis (1976). *European Journal of Pharmacology* 38, 269–273.

Satoh, T. (1971). *Brain Research* 28, 576–578.

Schwartz, J.C. (1975). *Life Science* 17, 503–518.

Shippenberg, T.S. et al. (2000). *Journal of Neurochemistry* 75, 258–265.

Solms, M. (2000). *Behavioral and Brain Sciences* 23, 843–850.

Steriade, M. & R.W. McCarley (1990). *Brainstem Control of Wakefulness and Sleep*. New York: Plenum Press.

Takeuchi, T. et al. (1999). *Sleep Research Online 2* (suppl 1), 279.

Takeuchi, T. et al. (2001). *Journal of Sleep Research 10*, 43–52.

Thompson, D.F. & D.R. Pierce (1999). *Annals of Pharmacotherapy* 33, 93–98.

Trulson, M.E. & D.W. Preussler (1984). *Experimental Neurology* 83, 367–377.

Vanni-Mercier, G. et al. (1984). *Comptes Rendus de l'Academie des Sciences* 298, 195–200.

Wikler, A. (1952). *Proceedings of the Society of Experimental Biology and Medicine* 79, 261–265.

Drug-Induced Alterations in Consciousness

CHAPTER 9

General anesthetics

Pamela Flood

1. Introduction

General anesthetic drugs have the ability to reduce the level of consciousness
in a dose dependent fashion. The study of the neurobiological mechanisms of
action of these drugs may provide insight into the systems that are necessary for
the existence of consciousness. It clearly cannot be assumed however, that the
systems that underlie the action of these substances are in themselves sufficient
for consciousness. Indeed, within a complex neural network, any number of
small alterations can disturb the whole. This chapter focuses on what is known
about the molecular mechanism of action of drugs that are used clinically for
general anesthesia.

General anesthesia is easily recognized but difficult to describe. Anesthe-
sia is a complex group of behaviors that allows for the conduct of surgery.
The most common anesthetic endpoint is immobility, commonly called MAC
(minimum alveolar concentration of a volatile drug to prevent purposeful mo-
tion in response to a noxious stimulus). MAC is a population EC_{50} for volatile
anesthetic induced immobility. If immobility were the only important anes-
thetic behavior however, adequate anesthesia could be produced with muscle
relaxants such as curare, despite the fact that they cause muscle paralysis with
complete awareness and sensitivity to pain. Indeed, the withdrawal response
induced in MAC studies is largely a spinal reflex (Antognini & Schwartz, 1993).
The goat has been used as a model to study the neuroanatomical basis of gen-
eral anesthetic induced immobility because of its unusual circulatory system.
The circulation of the goat is unique in that there is no internal carotid artery.
Thus the circulation to the brain can be separated from the circulation to the
spinal cord and body by separately perfusing the vertebral arteries. When a
goat spinal cord is perfused with a MAC concentration of isoflurane and the
brain is provided a sedating concentration of isoflurane (0.3 vol %) the goat

appears awake, blinks its eyes, but does not respond to a tail clamp (Antognini & Schwartz, 1993). In contrast, when the spinal cord and body is perfused with 0.3% isoflurane, and the brain a MAC concentration, the goat appears to be asleep, but will still respond to painful stimulus (Antognini & Schwartz, 1993).

While immobility is the most commonly measured anesthetic endpoint, a complete anesthetic also includes amnesia, analgesia, hypnosis and autonomic stability. Hypnosis and amnesia primarily relate to consciousness. It is interesting to note that concentrations of anesthetic drugs that induce hypnosis are typically only half the concentrations required for immobility (Gong et al., 1998). Anesthetic drug concentrations required for amnesia are approximately half again those required for hypnosis (Sonner et al., 1998). This fortuitous relationship is responsible for the rarity of awareness under anesthesia using typical anesthetic drugs. The incidence of awareness under anesthesia has been estimated at 0.18% when muscle relaxants such as curare are used as a part of the anesthetic and 0.10% when muscle relaxants are not used (Sandin et al., 2000).

The volatile anesthetics, ether and its analogs enflurane, isoflurane, sevoflurane and desflurane and the chemically similar alkane, halothane are considered "total anesthetics" as they each provide immobility, amnesia, analgesia, hypnosis and autonomic stability, the full panel of anesthetic effects. Other general anesthetic drugs such as the barbiturates, propofol, etomidate and ketamine provide some anesthetic effects but not others and are typically used in combination with other drugs. Comparison of the molecular mechanisms of these drugs with their behavioral profiles may be instructive in identifying which anesthetic target is related to a particular behavior.

Drugs that produce general anesthesia are structurally diverse (Fig. 1). It is remarkable that structures including alkanes, phenols, ethers, alcohols and a noble gas (Xenon) can produce similar states of consciousness. As a general rule, anesthetics are hydrophobic molecules. It was originally proposed by Overton and Meyer at the turn of the 20th century, that the hydrophobicity of a substance is directly correlated with it's potency as an anesthetic. (Meyer, 1899; Overton, 1901) This observation remains true today within classes of anesthetic compounds although the interpretation has changed (Janoff et al., 1981). Based on this observation the concept arose that general anesthetics produce anesthesia due to direct non-specific interaction with membrane lipid.

2. Non-specific intercolation of anesthetics into the lipid bilayer cannot cause anesthesia

Although an increase in membrane fluidity caused by anesthetic intercalation into the lipid bilayer was thought to result in general anesthesia, this theory was flawed in the following ways:

1. Several general anesthetics (isoflurane, ketamine, thiopental, etomidate) have one or more chiral carbons and thus exist as pairs of stereoisomers. In many cases one stereoisomer is more potent than the other at providing anesthesia despite little difference in pharmacokinetics (Christensen & Lee, 1973; Benthuysen et al., 1989; Harris et al., 1992; Dickinson et al., 1994). The stereoisomers have equal hydrophobic properties and partition equally into the membrane.
2. The increase in membrane fluidity at clinically relevant anesthetic concentrations is quite small. In fact, it is mimicked by a one degree increase in temperature (Franks & Lieb 1994). Clearly consciousness is not lost in states of low-grade fever.
3. As the carbon chain length in an anesthetic series increases (for example in the family of long chain alcohols), a substance becomes more hydrophobic and should be a more potent anesthetic. This is true only until a specific size cut off when the next larger agent becomes ineffective as an anesthetic (Franks & Lieb 1986).
4. It is true that a more hydrophobic anesthetic is more potent, but not all hydrophobic substances are anesthetics. There exist substances such as 1,2-dichlorohexafluorocyclobutane and 2, 3-dichlorooctafluorobutane that would be predicted to be anesthetic based on their hydrophobicity, but that do not have anesthetic properties. These substances are called either non-anesthetics or non-immobilizers depending on the behaviors that have been tested and found lacking (Koblin et al., 1994).

In the early 1980's, Franks and Lieb demonstrated that volatile anesthetic drugs could interact potently and specifically at a protein target, firefly luciferase (Franks and Lieb 1984). Clearly, activity on firefly luciferase was not the mechanism of general anesthesia as it is not present in man. However, in the intervening years several putative protein targets have been described primarily on the basis of being modulated in a clinically relevant concentration range and being appropriately located anatomically in relevant species. The question remains however, which protein interaction is important for anesthetic behavior? The rapidity of onset and ready reversibility of anesthetic action in vivo

and in vitro has pointed toward membrane proteins as general anesthetic targets. It had been known since the 1960s that general anesthetics inhibit synaptic transmission (Garfield et al., 1968). In principle, synaptic transmission might be reduced in several ways. Anesthetics might act to inhibit action potential propagation and thus reduce the activation of the synapse. Alternatively, the proteins that mediate synaptic transmission might be the targets of general anesthetic action.

3. Voltage gated ion channels

There is little effect on any aspect of action potential propagation at clinically relevant anesthetic concentrations (Franks & Lieb 1994). The action of many general anesthetic drugs has been studied at voltage gated ion channels that underlie the propagation of the action potential. Despite the lack of alteration of action potential propagation by general anesthetics, there is some evidence that some types of sodium channels might be affected at clinically relevant drug concentrations (Ratnakumari et al., 2000). Most voltage gated potassium channels are insensitive to general anesthetics at clinically used concentrations (Franks & Lieb 1994). However there is an interesting exception: TASK-1, a potassium channel that is strongly modulated by pH is directly activated by both halothane and sevoflurane at and below the clinical EC_{50s} for these drugs (Sirois et al., 2000; Talley et al., 2000). As TASK-1 has a role in setting the membrane potential in some cells, activation of this potassium current causes neuronal hyperpolarization and a reduction in action potential firing frequency (Sirois et al., 2000; Talley et al., 2000)

4. Ligand gated ion channels

In contrast to the limited role for modulation of voltage gated ion channels, the ligand gated ion channels that mediate and modulate synaptic transmission in the CNS are sensitive targets of general anesthetics. The recent explosion in the cloning of the genes for the protein subunits that form the ligand gated ion channels has led to the identification of the subunit composition of ligand gated ion channels that are modulated by general anesthetics. The ligand gated ion channel "family" has been subdivided into ion channels with four membrane traversing segments. Muscle nicotinic, neuronal nicotinic, $GABA_A$, glycine, serotonin, and glutamate receptors subunits traverse the membrane
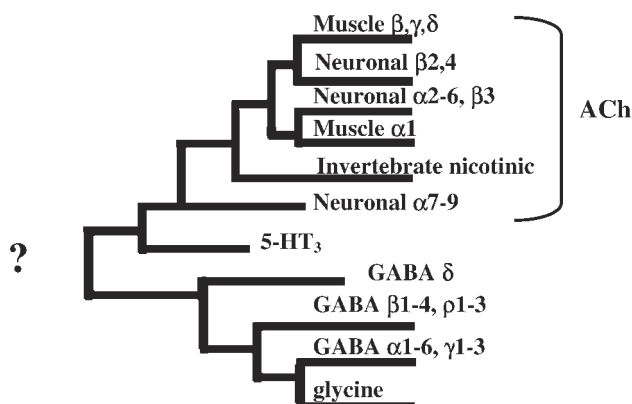
Figure 1. The evolutionary relationship between ligand-gated ion channels with four membrane spanning domains (modified from Flood, P. "Effects of Volatile Anesthetics at Nicotinic Acetylcholine Receptors." In *Molecular Bases of Anesthesia.* (2001) Ed. E. Moody and P. Skolnick; CRC Press, New York: p. 306).

three times and contain a "P loop" that forms the pore domain. Every general anesthetic in use today acts on at least one type and in some cases several types of ligand gated ion channels (Franks & Lieb 1994; Harrison & Flood 1998).

4.1 Receptors for GABA and glycine

Many general anesthetics act to potentiate the peak activation of $GABA_A$ and glycine receptors by low concentrations of agonist (Table 1). General anesthetic drugs act to increase the $GABA_A$ receptor affinity for agonist at low agonist concentrations. They also prolong current decay resulting in an increase in current density. Inhibitory Post Synaptic Currents (IPSCs) are prolonged by both pentobarbital and halothane at clinically relevant concentrations (Lukatch & MacIver, 1997). The commonality of potentiation of the $GABA_A$ response has lead to an inaccurate concept that the $GABA_A$ receptor is the principal receptor for general anesthesia. However, all general anesthetics do not potentiate the response to GABA. Ketamine, nitrous oxide (N_2O) and xenon have little affect on $GABA_A$ receptor activation (Flood & Krasowski, 2000; Yamakura et al., 2000; Yamakura & Harris, 2000). Thus, potentiation of inhibitory synaptic transmission is a possible mechanism for general anesthesia but is not the only mechanism. The benzodiazepines are well known GABA potentiating drugs, but they do not act as general anesthetics except very high concentrations. If the behavioral effects of a benzodiazepine and propofol are compared at concen-

Table 1. The modulatory effect of general anesthetic drugs on ligand-gated ion channels. The effect of clinically relevant concentrations of general anesthetic drugs. + indicates potentiation, 0 indicates no significant effect in the majority of studies and – indicates inhibition of activation. ? indicates insufficient data is available.
(modified from: Krasowski, MD and Harrison, NL General Anesthetic Actions on Ligand Gated Ion Channels. (1999) *Cell Mol Life Science, 55*: 1287–1303).

Intravenous Anesthetics	GABA$_A$	glycine	GABA$_C$	Muscle nAChR	Neuronal nAChR	5HT$_3$	AMPA	Kainate	NMDA
Ketamine	0	0	?	0	–	0	0	0	–
Barbiturates	+	0	0	0	–	0	–	–	0
Propofol	+	+	0	0	0	0	0	0	0
Etomidate	+	0	0	0	0	0	0	0	0
Alphaxalone	+	0	0	0	0	0	0	0	0

Inhaled Anesthetics	GABA$_A$	glycine	GABA$_C$	Muscle nAChR	Neuronal nAChR	5HT$_3$	AMPA	Kainate	NMDA
Enflurane	+	+	0	–	–	+	–	+	0
Halothane	+	+	0	0	-	+	–	+	0
Isoflurane	+	+	0	0	–	+	–	+	0
Sevoflurane	+	+	0	0	–	?	?	?	?
Nitrous Oxide	0	?	?	–	–	?	0	?	–
Xenon	0	?	?	–	–	?	0	?	–

trations that cause equivalent potentiation of the response to GABA, propofol will cause anesthesia while the benzodiazepine will only cause sedation.

Recently, individual amino acid residues have been identified that are required for anesthetic action at GABA$_A$ and glycine receptors. Two amino acid residues, located at homologous positions on the extracellular portions of TM2 and TM3 of the alpha subunit, are required for isoflurane and enflurane potentiation of GABA$_A$ receptor function (Mihic et al., 1997). An amino acid residue, homologous to the residue in TM2 of the alpha subunit that was implicated in volatile anesthetic action has been identified in the beta subunit of the GABA$_A$ receptor as important for the action of propofol and etomidate and neurosteroid action (Belelli et al., 1996; Moody et al., 1997; Pistis et al., 1997; Krasowski et al., 1998; McGurk et al., 1998). An additional amino acid residue in the N-terminal portion of TM1 of the beta subunit has been implicated in both agonist sensitivity and the potentiation of agonist binding and activation by etomidate, propofol, alphaxalone and pentobarbital (Carlson et al., 2000).

The indication of interaction with specific amino acid residues in the $GABA_A$ and glycine receptors strongly suggests direct anesthetic protein interactions.

A next logical step in connecting the modulation of a particular protein target to the mediation of anesthetic behavior may be the study of genetically modified animals bearing specific mutations of receptor in question. "Conditional knockouts" in which the protein in question is present during development and is interrupted only when a particular condition is met (i.e. the animal is given tetracycline) would appear superior to constitutive knockouts, which influence development. However, the production of other forms of the protein or other complementary proteins can be affected as a consequence of the lack of the missing protein.

Animals with the deletion of specific $GABA_A$ subunits have been studied for behavior under anesthesia. The $GABA_A$ receptors are made up of a large family of α, β and γ subunits that form heterometic receptors. It is unlikely that an animal with all $GABA_A$ receptors deleted would be viable as animals with total pharmacological GABA blockade by bicuculin and picrorotoxin suffer from intractable seizures. Mice with constitutive disruption of the GABA receptor α6 and β3 subunits have been studied for anesthetic sensitivity. Mice lacking β3 GABA subunits during development are born with cleft lip and palate, epilepsy, hypersensitive behavior and have extensive neonatal mortality (Homanics et al., 1997). The have mildly reduced motor response to the general anesthetics enflurane and halothane, but no change in the concentration required for the loss of consciousness (Quinlan et al., 1998). GABA β3 knockout mice had reduced sleep times with etomidate and midazolam but not pentobarbital (Quinlan et al., 1998). The β3 subunit of the $GABA_A$ receptor may thus have a role in hypnosis caused by etomidate and midazolam but not pentobarbital. Mice lacking the GABA α6 subunit have normal behavioral responses to midazolam and volatile anesthetics (Homanics et al., 1997).

4.2 Nicotinic receptors

Nicotinic acetylcholine receptors (nAChRs) from muscle and the electric organ of torpedo Electroplax have been studied for many years as a model ligand gated ion channel system. From these classical studies it is clear that volatile (Lechleiter & Gruener, 1984; Pocock & Richards, 1988; Wachtel & Wegrzynowicz, 1991; Dilger et al., 1993; Wachtel, 1995; Scheller et al., 1997) and intravenous (Wachtel & Wegrzynowicz, 1992; de Armendi et al., 1993; Yost & Dodson, 1993; Scheller et al., 1996) anesthetics inhibit the function of nAChRs albeit at high clinical concentrations. Inhibition of the postsynaptic nicotinic re-

ceptor in skeletal muscle may be responsible for muscle relaxation seen clinically at high concentrations of these drugs.

Neuronal nicotinic receptors consist of a heterogeneous group of subunits that rivals the GABA$_A$ receptors in complexity and diversity (reviewed by McGehee & Role, 1995). Brain nAChRs have both pre and post synaptic roles in synaptic transmission. They function as postsynaptic receptors on inhibitory interneurons in the hippocampus (Alkondon et al., 1998; Frazier et al., 1998a; Frazier et al., 1998b) and nAChRs function as excitatory presynaptic receptors where their activation increases the probability of the release of other neurotransmitters including glutamate, GABA, dopamine and acetylcholine itself (MacDermott et al., 1999). The nAChRs are thus anatomically situated such that their inhibition by general anesthetics could cause global changes in multiple neuronal networks that might underlie anesthetic induced behavior.

It has been known for many years that the general anesthetics halothane and pentobarbital inhibit synaptic transmission mediated by acetylcholine in the sympathetic nervous system (Nicoll, 1978; Bosnjak et al., 1982). Ketamine inhibits nicotinic transmission at the renshaw synapse in the spinal cord (Lodge et al., 1982). More recently with the cloning of 9 alpha and 3 beta subunits that combine to form the nAChRs expressed in brain, the molecular nature of nicotinic inhibition has been elucidated. Alpha 2–6 subunits combine with beta subunits to make heteromeric nAChRs. Alpha 7–9 subunits can form homomeric nAChRs (when heterologously expressed) (McGehee & Role, 1995). The volatile anesthetics isoflurane, halothane and sevoflurane inhibit the activation of heteromeric nAChRs, while homomeric α7 nAChRs are relatively unaffected (Flood et al., 1997; Violet et al., 1997). The intravenous anesthetics ketamine and thiopental inhibit both heteromeric and homomeric nAChRs (Downie et al., 2000; Flood & Krasowski, 2000; Yamakura et al., 2000). Neurosteroid based anesthetic drugs inhibit the activation of nAChRs composed of α4 and β2 subunits (Sabey et al., 1999). However, the nAChRs can not be construed as a common receptor for general anesthetic drugs, since the intravenous anesthetics etomidate and propofol that potentiate the activity of GABA have little effect at nAChRs at clinically relevant concentrations (Flood & Role, 1997; Flood & Krasowski, 2000). Inhibition of the nAChRs expressed in the central nervous system is thus common to many, but not all general anesthetic drugs.

4.3 Ionotropic receptors for glutamate

Excitatory synaptic transmission in the central nervous system is largely glutamatergic. There is ample evidence for inhibition of excitatory transmission

in the brain and spinal cord by general anesthetics, but this inhibition is largely presynaptic (Collins et al., 1995; Schlame & Hemmings, 1995; MacIver et al., 1996; Buggy et al., 2000). The central receptors for glutamate have been traditionally separated by their response to pharmacological agonists into those sensitive to alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA), kainate and N-methyl-D-aspartate (NMDA). The volatile anesthetics isoflurane, halothane and enflurane inhibit the responses of AMPA receptors while they potentiate kainate responses at high clinical concentrations (Wakamori et al., 1991; Carla & Moroni, 1992; Minami et al., 1998). The latter effect is likely to be minor as in vivo there are mostly alterations in glutamate release rather than a postsynaptic effect with volatile anesthetics. The barbiturate pentobarbital inhibits AMPA receptors (Dildy-Mayfield et al., 1996). The kainate response in hippocampal neurons from mice with GLUR2 (an AMPA receptor) deletion is less inhibited by pentobarbital, but the mice are paradoxically more sensitive to anesthesia by barbiturates (Joo et al., 1999). Thus the inhibition of the kainate response by pentobarbital does not cause hypnosis (Joo et al., 1999).

NMDA responses are not affected by volatile anesthetics (Wakamori et al., 1991; Carla & Moroni, 1992). In contrast, NMDA responses are potently inhibited by the intravenous anesthetic ketamine and the gaseous anesthetics nitrous oxide and Xenon (Lodge et al., 1982; Anis et al., 1983) (Jevtovic-Todorovic et al., 1998; Mennerick et al., 1998; Yamakura & Harris, 2000). AMPA and kainate responses are largely unaffected by ketamine, nitrous oxide and xenon (Anis et al., 1983; Yamakura & Harris, 2000). In contrast to the questionable clinical significance of AMPA and kainate receptor inhibition by volatile anesthetics and barbiturates, the inhibition of NMDA receptors by ketamine, nitrous oxide and xenon is likely central to the hypnotic and analgesic affects of these drugs.

5.   Metabotropic receptors

Metabotropic G-protein linked receptors are also modulated by general anesthetics. In particular, the current produced through activation of muscarinic receptors (M1) for acetylcholine and the serotonergic receptor $5HT_2$ is inhibited by halothane, isoflurane and enflurane (Lin et al., 1993; Minami et al., 1994; Durieux, 1995). Ketamine inhibits muscarinic receptors although there is no stereospecificity of inhibition (Durieux & Nietgen, 1997). The S-isomer of ketamine is more potent as an anesthetic than the R-isomer (Benthuysen et al., 1989). It is thus unlikely that the M1 muscarinic receptor plays a role in

at least immobility produced by ketamine. The role of muscarinic inhibition in volatile anesthetic action is unclear as the broad-spectrum antimuscarinic drug atropine is used commonly in anesthesia and has no effect on MAC. Centrally acting antimuscarinic drugs such as atropine have been used historically for their hallucinogenic properties (Itil & Fink, 1968). Atropine is used at much lower concentrations in modern anesthetic practice, not for its central effects, but to prevent bradycardia and excessive salivation caused by other drugs. In fact, glycopyrolate, another antimuscarinic agent that does not cross the blood brain barrier is often substituted for atropine today.

Metabatropic receptors for glutamate, particularly mGluR1 and mGluR5, are important modulators of synaptic transmission in the central nervous system and are involved in learning and memory (Christoffersen et al., 1999). Halothane inhibits the current generated through activation of mGluR5, but not mGluR1. The guanine nucleotide-binding protein activity was selectively reduced (Lin et al., 1993). An increase in PKC mediated phosphorolation caused by halothane is thought to result in inhibition (Minami et al., 1998). Further evidence of the potential role of metabatropic glutamate receptors can be derived from their response to non-immobilizers. As discussed previously, non-immobilizers are drugs that would be predicted to cause immobility based on their hydrophobicity but do not (Koblin et al., 1994). The non-immobilizers, 1,2-dichlorohexafluorocyclobutane (F6) and 2,3-chlorooctafluorobutane (F8) are similar in that they do not cause immobility at any soluble concentration, while the related compound 1-chloro-1,2,2-triflurocyclobutane (F3) is anesthetic. F6 but not F8 inhibits learning and memory (Kandel et al., 1996; Sonner et al., 1998). The anesthetics, halothane and F3 the function of MGluR5, F6 inhibited both MGluR5 and MGluR1 while F8 did not affect the currents generated by the activation of either receptor (Minami et al., 1998). These results, taken together, suggest that the inhibition of MGluR5 by anesthetics may be related to amnesia, but not immobility.

6.   Conclusions

A state of consciousness depends on the intact function of the complex neural networks that underlie alertness, learning and memory. General anesthetics appear to interrupt synaptic transmission within these systems. Multiple ion channels and receptors that mediate and modulate synaptic transmission are putative targets for general anesthetics. All general anesthetics are not alike in the way they alter consciousness. For example, ketamine induces a state of

consciousness that is different from that induced by other anesthetics. "Ketamine as a sole anesthetic produces a cataleptic state with nystagmus and intact corneal and light reflexes" (Miller, 1994). Ketamine is also the only anesthetic that does not potentiate GABA$_A$ receptors in a clinically relevant range, with the exception of nitrous oxide and xenon, which though less extensively studied appear to also act at NMDA and nicotinic receptors. It may be useful to separate anesthetics into two partially overlapping groups, one including ketamine, nitrous oxide and xenon that act on NMDA and nicotinic receptors and a second group including anesthetics that significantly potentiate the response to GABA.

The anesthetic state achieved with ketamine is better termed 'inattentiveness to surroundings' than 'unconsciousness'. With volatile anesthetics, that inattentiveness is perhaps overshadowed by unconsciousness during the anesthetic, but can be appreciated on emergence from anesthesia. Patients typically awaken from a general anesthetic with, for example, 0.2% isoflurane end tidal, measured by a gas analyzer (about 56 μM in solution). At this concentration, there remains approximately 20% central nicotinic inhibition, while GABA$_A$ potentiation is at threshold. (Harrison et al., 1993; Flood et al., 1997). Drugs that do not inhibit nAChRs in a clinically relevant range, particularly propofol, are notable for the lack of inattentiveness and dysphoria on emergence from anesthesia. Prolonged inattentiveness, dysphoria and perhaps other side effects of ketamine, and volatile anesthetics may be due to lingering nicotinic blockade. Particularly elderly patients and those suffering from Alzheimer's or Parkinson's disease, who have impaired central nicotinic systems, often emerge from anesthesia, inattentive, disoriented and dysphoric. (Golden et al., 1989; Miller, 1994). A common treatment for this "emergence delirium" is physostigmine, an acetylcholinesterase inhibitor that would increase the concentration of acetylcholine in the brain. These patients may represent a subgroup, which due to preexisting abnormalities in their central cholinergic system is particularly sensitive to nicotinic blockade by general anesthetics. It may be that this is a group of patients in which it is best to avoid general anesthetics that inhibit nAChRs. This area warrants further study and consideration.

Comparison of patterns of ligand-gated ion channel modulation with patterns of anesthetic behavior results in several hypotheses. The inhibition of nAChRs by general anesthetics may mediate analgesia, as well as inattentiveness and delirium. GABA$_A$ augmentation may lead to a particular state of unconsciousness. Validation of these hypotheses and the definition of the central circuitry in which they occur will require further experiments. If these hypotheses prove valid, the designers of future anesthetic drugs will be able

to test agents on heterologously expressed ion channels in order to design *in* the desirable and *out* the undesirable behavioral responses in humans. In addition, future research, utilizing genetically modified animals that express the mutations making the target insensitive to general anesthetics while still being sensitive to their native agonist will allow the association of specific targets with specific behaviors.

References

Alkondon, M. et al. (1998). *Brain Research* 810, 257–623.

Anis, N.A. et al. (1983). *British Journal of Pharmacology* 79, 565–575.

Antognini, J.F. & K. Schwartz (1993). *Anesthesiology* 79, 1244–1249.

Belelli, D. et al. (1996). *British Journal of Pharmacology* 118, 563–576.

Benthuysen, J.L. et al. (1989). *Neuropharmacology* 28, 1003–1009.

Bosnjak, Z.J. et al. (1982). *Anesthesiology* 57, 473–479.

Buggy, D.J. et al. (2000). *Anesthesiology* 92, 1067–1073.

Carla, V. & F. Moroni (1992). *Neuroscience Letters* 146, 21–24.

Carlson, B.X. et al. (2000). *Molecular Pharmacology* 57, 474–484.

Christensen, H.D. & I.S. Lee (1973). *Toxicology and Applied Pharmacology* 26, 495–503.

Christoffersen, G.R. et al. (1999). *Behavioural Brain Research* 101, 215–226.

Collins, J.G. et al. (1995). *Trends in Neurosciences* 18, 549–553.

de Armendi, A.J. et al. (1993). *Anesthesiology* 79, 1033–1041.

Dickinson, R., N.P. et al. (1994). *Biophysics J.* 66, 2019–2023.

Dildy-Mayfield, J.E. et al. (1996). *Journal of Pharmacology and Experimental Therapeutics* 276, 1058–1065.

Dilger, J.P. et al. (1993). *Molecular Pharmacology* 44, 1056–1063.

Downie, D.L. et al. (2000). *Anesthesiology* 93, 774–783.

Durieux, M.E. (1995). *Anesthesiology* 82, 174–182.

Durieux, M.E. & G.W. Nietgen (1997). *Anesthesiology* 86, 1326–1333.

Flood, P. & M. Krasowski (2000). *Anesthesiology* 92, 1418–1425.

Flood, P. et al. (1997). *Anesthesiology* 86, 859–865.

Flood, P. & L. Role (1997). *Neuroscience Abstracts* 23, 915.

Franks, N. & W. Lieb (1994). *Nature* 367, 607–614.

Franks, N. P.& W.R. Lieb (1984). *Nature* 310, 599–601.

Franks, N.P. & W.R. Lieb (1986). *Proceedings of the National Academy of Sciences USA* 83, 5116–5120.

Frazier, C.J. et al. (1998a). *Journal of Neuroscience* 18, 8228–8235.

Frazier, C.J. et al. (1998b). *Journal of Neuroscience* 18, 1187–1195.

Garfield, J.M. et al. (1968). *Anesthesiology* 29, 79–92.

Golden, W., R. et al. (1989). *Annals of Internal Medicine* 111, 218.

Gong, D.H. et al. (1998). *Anesthesia and Analgesia* 86, 198–201.

Harris, B., E. et al. (1992). *European Journal of Pharmacology* 217, 215–216.

Harrison, N. & P. Flood (1998). *Science & Medicine* 5, 18–27.

Harrison, N.L. et al. (1993). *Molecular Pharmacology* 44, 628–632.

Homanics, G.E. et al. (1997). *Proceedings of the National Academy of Science USA* 94, 4143–4148.

Homanics, G.E. et al. (1997). *Molecular Pharmacology* 51, 588–596.

Itil, T. & M. Fink (1968). *Progress in Brain Research* 28, 149–168.

Janoff, A.S. et al. (1981). *Biochimica Biophysica Acta* 649, 125–128.

Jevtovic-Todorovic, V. et al. (1998). *Nature Medicine* 4, 460–463.

Joo, D.T. et al. (1999). *Anesthesiology* 91, 1329–1341.

Kandel, L. et al. (1996). *Anesthesia and Analgesia* 82, 321–326.

Koblin, D.D. et al. (1994). *Anesthesia and Analgesia* 79, 1043–1048.

Krasowski, M.D. et al. (1998). *Neuroscience Letters* 240, 81–84.

Lechleiter, J. & R. Gruener (1984). *Proceedings of the National Academy of Sciences of the United States of America* 81, 2929–2933.

Lin, L. et al. (1993). *Molecular Pharmacology* 43, 941–948.

Lodge, D. et al. (1982). *Neuroscience Letters* 29, 281–286.

Lukatch, H.S. & M.B. MacIver (1997). *Brain Research* 765, 108–112.

MacDermott, A.B. (1999). *Annual Review of Neuroscience* 22, 443–485.

MacIver, M.B. (1996). *Anesthesiology* 85, 823–834.

McGehee, D.S. & L.W. Role (1995). *Annual Review of Physiology* 57, 521–546.

McGurk, K.M. et al. (1998). *British Journal of Pharmacology* 123, 1–8.

Mennerick, S.V. et al. (1998). *Journal of Neurosciences* 18, 9716–9726.

Meyer, H. (1899). *Naunyn-Schmiedeberg's Archives of Experimental Pathologi Pharmakology* 42, 109–118.

Mihic, S.J. et al. (1997). *Nature* 389, 385–389.

Miller, E. (1994). *Anesthesiology*. New York, Churchill Livingstone.

Minami, K.R.W. et al. (1998). *Molecular Pharmacology* 53, 148–156.

Minami, K.M.J. et al. (1998). *Journal of Biological Chemistry* 273, 8248–8255.

Minami, K.N. et al. (1994). *Naunyn-Schmiedebergs Archives of Pharmacology* 349, 223–229.

Moody, E.J. et al. (1997). *Journal of Neurochemistry* 69, 1310–1313.

Nicoll, R.A. (1978). *Science* 199, 451–452.

Overton, E. (1901). *Studien uber die Narkose, zugleich ein Beitrag zur allgemeiner Pharmakologie*. Jena, Switzerland, Gustave Fischer.

Pistis, M. et al. (1997). *British Journal of Pharmacology* 122, 1707–1719.

Pocock, G. & C.D. Richards (1988). *British Journal of Pharmacology* 95, 209–217.

Quinlan, J.J. et al. (1998). *Anesthesiology* 88, 775–780.

Ratnakumari, L. et al. (2000). *Anesthesiology* 92, 529–541.

Sabey, K. et al. (1999). *Molecular Pharmacol* 55, 58–66.

Sandin, R. et al. (2000). *Lancet* 355, 707–711.

Scheller, M. et al. (1996). *Anesthesia and Analgesia* 83, 830–836.

Scheller, M. et al. (1997). *Anesthesiology* 86, 118–127.

Schlame, M. & H.C. Jr. Hemmings (1995). *Anesthesiology* 82, 1406–1416.

Sirois, J.E. et al. (2000). *Journal of Neuroscience* 20, 6347–6354.

Sonner, J.M. et al. (1998). *Anesthesia and Analgesia* 87, 200–205.

Talley, E.M. et al. (2000). *Neuron* 25, 399–410.

Violet, J.M. et al. (1997). *Anesthesiology* 86, 866–874.

Wachtel, R.E. (1995). *Journal of Pharmacology & Experimental Therapeutics* 274, 1355–1361.

Wachtel, R.E. & E.S. Wegrzynowicz (1991). *Annals of the New York Academy of Sciences* 625, 116–128.

Wachtel, R.E. & E.S. Wegrzynowicz (1992). *Br. J. Pharmacol.* 106, 623–627.

Wakamori, M.Y. et al. (1991). *Journal of Neurophysiology* 66, 2014–2021.

Yamakura, T. et al. (2000). *Anesthesiology* 92, 1144–1153.

Yamakura, T. & R.A. Harris (2000). *Anesthesiology* 93, 1095–1101.

Yost, C.S. & B.A. Dodson (1993). *Cellular & Molecular Neurobiology* 13, 159–172.

CHAPTER 10

Effects of drugs on sleep

Heather Ashton

1. Introduction

The most dramatic natural changes in the level of consciousness are those that occur between waking and sleeping. As described in Chapters 6, 7 and 8, sleep itself comprises several different levels of consciousness including light sleep (Stages 1 and 2), deeper SWS of non-REM sleep, and the relatively activated state of REM sleep, often associated with dreaming. These various stages of sleep can be radically influenced by drugs. A selection of such drugs are mentioned here (for further reviews see Ashton, 1994; Ashton and Young, 1998; Buysse, 1991).

2. Anxiolytics, sedatives, hypnotics (benzodiazepines, barbiturates, chloral derivatives, chlormethiazole, zopiclone, zolpidem)

In acute dosage, all these drugs hasten sleep onset, decrease nocturnal awakenings, increase total sleeping time and often impart a sense of deep and refreshing sleep. However, all have profound effects on sleep stages. Light sleep (Stage 2) is prolonged and mainly accounts for the increased sleeping time. By contrast, the duration of both SWS and REM sleep may be considerably reduced. Dreaming is diminished. However, tolerance to these effects develops after a few days or weeks of regular use and sleep patterns tend to return to pre-drug levels. On withdrawal after chronic use, the effects on sleep are reversed and a withdrawal syndrome with rebound insomnia, frequent awakenings, vivid dreams and nightmares is common. With rapidly eliminated drugs, this rebound may occur in the latter part of the night.

The effects of benzodiazepines, and drugs with similar actions, result from interactions with benzodiazepine binding sites on the $GABA_A$ receptor com-

plex, causing enhancement of GABA activity in the brain (Haefely, 1990). There are copious GABA/benzodiazepine receptors in the reticular formation, limbic system and cerebral cortex and GABA-enhancement in these areas is thought to account for the hypnotic effects. Secondary effects, such as decreased release of acetylcholine and monoamines (Haefely, 1990) may cause the changes in REM sleep. With chronic use, "down-regulation" of GABA receptors occurs (due to decreased affinity for GABA), and on withdrawal a state of GABA-underactivity is exposed, leading to the withdrawal syndrome.

3. Alcohol

Acute use of alcohol at bedtime reduces sleep latency, decreases REM sleep and increases SWS. Later in the night, following metabolism of the alcohol, rebound effects occur with frequent arousals, increased REM sleep, and vivid dreams and nightmares, accompanied by tachycardia and sweating. In chronic alcoholics sleep is markedly fragmented and punctuated by frequent awakenings. Alcohol withdrawal further disrupts sleep with dreams and nightmares and light fragmented sleep. Alcohol acts similarly to benzodiazepines by augmenting GABA-mediated central inhibition, as well as exerting inhibitory effects on glutamate activity and decreasing release of acetylcholine and monoamines. The effects on sleep result from these effects.

4. Amphetamine and related compounds (dexamphetamine, methylphenidate, ephedrine, MDMA [ecstasy], cocaine and other dopaminergic drugs)

All these drugs reduce sleep duration, decrease SWS and REM sleep, increase sleep latency and increase sleep fragmentation. They can cause a dose-related insomnia during use, and hypersomnia with increased dreaming and nightmares on withdrawal after chronic use.

The effects on sleep result from the psychostimulant and sympathomimetic actions of these drugs. They enhance noradrenergic, dopaminergic and serotonergic transmission in the central and peripheral nervous system mainly by increasing transmitter release and also inhibitory uptake.

5.   Caffeine, theophylline

Caffeine and theophylline decrease total sleep time, time spent in SWS and REM sleep and increase the number of intrasleep arousals. Withdrawal of caffeine in regular users leads to daytime sleepiness, increased slow wave (delta) activity on the EEG and headaches. The mechanism of action appears to be antagonism of central adenosine A_1 and A_2 receptors which normally exert a CNS depressant action, with consequent interference with the sleep-inducing action of adenosine (Chapter 6).

6.   Antidepressant drugs

Many antidepressant drugs have pronounced effects on sleep. Several tricyclic compounds (amitriptyline and others) have sedative actions while others (imipramine and others) are less sedative or even stimulant. Monoamine oxidase inhibitors (MAOIs) have central stimulant effects and may cause insomnia. Specific serotonin reuptake inhibitors (SSRIs) and combined serotonin, noradrenaline reuptake inhibitors (SNRIs) can also cause insomnia.

Nearly all antidepressants share the property of decreasing REM sleep, an action which has been shown for both tricyclics and MAOIs. The latter have been observed to cause complete suppression of REM sleep (Dunleavy & Oswald, 1973). Since REM sleep is increased in depression, this action tends to normalise sleep patterns in depressed patients. However, suppression of REM sleep does not necessarily coincide with improvement in mood, and the drugs also decrease REM sleep in normal volunteers. A rebound of REM sleep occurs on drug withdrawal after chronic use of antidepressants, with increased dreaming and nightmares. Most antidepressants, although they alleviate early morning waking in depressed patients, have little effect on SWS, although trazodone and nefazodone are reported to increase SWS in depressed patients and normal subjects.

The mechanisms of the sleep changes induced by antidepressants are probably multiple. Sedative effects may be due to anticholinergic actions (some tricyclics) or inhibition of α_2 receptors (mianserin, trazodone). Stimulant effects are probably due to inhibition of monoamine reuptake. This action, combined with anticholinergic activity, could explain the reduction in REM sleep by preventing the suppression of serotonergic and noradrenergic activity which occurs during this stage of sleep (Chapters 7 and 8).

7. Anticholinergic and cholinomimetic drugs

Cholinergic agonists and anticholinesterases increase wakefulness and arousal. Effects on sleep include nightmares in high doses, insomnia, decreased SWS and increased REM sleep. Conversely, anticholinergic drugs generally cause sedation, decreased REM sleep and sometimes increased SWS. These effects are due to interference with cholinergic mechanisms involved in arousal (Chapters 2, 3) and the induction or facilitation of REM sleep (Chapters 7, 8).

8. Antipsychotic drugs

Many antipsychotic drugs have sedative effects and can produce subjective sleepiness. These drugs tend to normalise the disrupted and fragmented sleep pattern of schizophrenic patients. They decrease wakefulness, increase total sleep time and increase SWS. Sleep is increased with low doses and decreased with higher doses. Insomnia may occur on antipsychotic withdrawal. The mechanism of action of these drugs is probably complex and includes antagonistic effects on monoaminergic systems as well as anticholinergic and antihistamine effects.

9. Antihistamines

Histamine H_1 receptor antagonists which enter the brain (diphenhydramine, promethazine and others) have sedative actions and polysomnographic recordings have shown that they suppress REM sleep and modestly increase SWS. A rebound in REM sleep sometimes occurs on discontinuation. Stimulation of central H_1 and H_2 receptors markedly potentiates signals produced by excitatory amino acids and it has been suggested that histamine acts as a "waking amine" (Schwartz et al., 1986). The effects of centrally acting antihistamines on sleep may be due to inhibition of these effects.

10. Conclusion

Consistent with alterations in neurotransmission associated with sleep onset, SWS and REM sleep (Chapters 6–8), drugs affecting neurotransmitter function have specific effects on the sleep-wake cycle. Thus reduced levels of conscious-

ness, sleep onset and SWS are promoted by cholinergic, dopaminergic and histamine antagonists; sleep duration is in contrast reduced by monoaminergic (noradrenergic and 5-HT) agonists and adenosine antagonists, and by cholinergic agonists. Cholinergic agonists appear to be unique in promoting REM sleep, which is inhibited by monoaminergic agonists. Antagonism of the GABA$_A$ receptor by for example benzodiazepines and barbiturates, while promoting sleep also decreases REM. This effect is likely to relate to inhibition of a range of neurons bearing this receptor type. As discussed in Chapter 9, the GABA$_A$ receptor is also target for several general anaesthetic agents. Chemicals modulating consciousness such as described in this and the previous chapter provide the most compelling arguments for an essential neurochemical basis of consciousness.

References

Ashton, H. (1994). In R. Cooper (Ed.), *Sleep* (175–211). London: Chapman & Hall Medical.

Ashton, C.H. & A.H. Young (1998). In D.M. Davies, R.E. Ferner & H. De Glanville (Eds.), *Davies' Textbook of Adverse Drug Reactions* (669–731). London: Chapman & Hall Medical.

Buysse, D.J. (1991). In T.H. Monk (Ed.), *Sleep, Sleepiness and Performance* (249–306). Chichester: John Wiley.

Dunleavy, D.L.F. & J. Oswald (1973). *Archives of General Psychiatry* 28, 353–366.

Haefely, W. (1990). In I. Hindmarch (Ed.), *Benzodiazepines: Current Concepts* (1–18). Chichester: John Wiley.

Schwartz, J.C. et al. (1986). *Trends in Pharmacological Sciences* 7, 24–28.

Chapter 11

Neuroleptics

Clive Ballard and Margaret Piggott

1. Introduction

Neuroleptic drugs, sometimes referred to as antipsychotics or major tranquillisers, are widely prescribed psychotropic agents. Historically, derived from antihistamines and used as adjuncts in anaesthesia, the use of these agents developed because of their effectiveness for the treatment of acute psychosis in schizophrenia and other psychotic disorders, and they are also widely used for the treatment of psychiatric and behavioural symptoms in people with dementia. Although the majority of conventional antipsychotic agents have a rich pharmacology, with effects on a number of receptor systems, the therapeutically effective dose appears to relate to the potency of D2 receptor blockade. This inherited wisdom has been challenged over the last decade with the introduction of atypical antipsychotics, which have comparable antipsychotic activity with lower levels of striatal D2 receptor blockade although they may have similar effects on cortical targets (Lidow & Goldman-Rakic, 1994). The exact mechanisms of action of these agents remain unclear, whilst most have both D1 and D2 receptor activity and many have 5-HT_{2A} receptor antagonism, drugs with exclusive D1 or 5-HT_{2A} antagonism have generally had less potent antipsychotic activity. As would be expected, the side effects include a number of symptoms related to striatal dopaminergic blockade, including extrapyramidal symptoms.

In this chapter, the primary focus is the dopaminergic actions of antipsychotic agents. When appropriate, brief reference is made to the neurochemistry of the dopaminergic system (covered in more detail in Chapters 1 and 5) and to other pharmacological agents manipulating dopaminergic parameters.

The impact of antipsychotic agents on consciousness is immediately apparent from the frequency with which sedation and drowsiness are reported as side effects (Tune et al., 1991), a property which historically has been used as a treat-

ment approach in the technique of modified narcosis (Walter et al., 1972). In psychiatrically normal subjects, there is characteristically a diminution in emotional responsiveness, indifference to environmental stimuli, and a reduction in initiative and spontaneous activity (Ashton, 1987). In addition, neuroleptics have been reported to be a cause of syncopal episodes (sudden transient loss of consciousness) in the elderly (Cherin et al., 1993) which may represent side effects generated at cortical or brainstem sites of action. There has also been some suggestion that antipsychotic agents may in some circumstances impact upon consciousness in several more specific ways.

The first form of altered consciousness, described in an anecdotal case series literature (e.g. Scharbach, 1978), indicates that some individuals may experience an "oneiric" state, defined in a standard phenomenology text as "an unsatisfactory term, not clearly differentiated from delirium. The patient is disturbed, confused, experiences elaborate hallucinations usually visual and impairment of consciousness. Marked emotional changes from terror to enjoyment occur, and the patient often appears as if in a dreamworld." Such states have also been described amongst people with schizophrenia who are drug free, hence it is unclear whether there is a specific relationship with antipsychotic agents. Reports of this phenomenon in response to butyrophenones (Scharbach, 1978) and after sudden withdrawal of L-dopa (Argenta et al., 1971) have supported the hypothesis that this may be a dopaminergically mediated phenomenon. Further systematic studies with tighter phenomenological definitions are however required to clarify the status of this possible syndrome.

The second form of altered consciousness pertains to the syndrome of lethal catatonia (Castillo et al., 1989), which in addition to the presence of symptoms rather similar to the neuroleptic malignant syndrome (discussed below), includes catatonic phenomena with clouding of consciousness. Catatonia is a disturbance of volition and movement, where people although awake may remain immobile for protracted periods and often appear as if frozen to the spot. Patients have a typical pattern of responses which include phenomena such as negativism and automatic obedience. It is unclear in the typical form whether this relates to a selective abnormality of consciousness, although in the context of lethal catatonia it is also accompanied by clouding of consciousness (Carroll & Taylor, 1997). Again, as this syndrome was first reported prior to the availability of antipsychotic agents (Castillo et al., 1989), it must in some people at least be a naturally occurring phenomena; although it is probably more frequent since the introduction of neuroleptics, with for example 17 clear cut

cases reported from the Iowa case register over an 8 year period (Carroll & Taylor, 1997).

In some patients with post encephalitic Parkinson's disease a long-standing catatonic state was reported and a dramatic raising of consciousness levels following the administration of L-dopa (Sachs, 1990). In these patients there is a devastating loss of dopaminergic neurons, including those in the ventral tegmental area. Since these neurons normally follow a continuous firing pattern throughout the sleep-wake cycle, perhaps they are involved in 'time-keeping'. Their loss could contribute to the lack of perception of the passage of time experienced by patients with post-encephalitic Parkinson's disease.

There are in addition, a group of conditions involving more global pathological alterations of consciousness in which dopaminergic dysfunction or alteration with medication appears to play an important role in consciousness.

2.   Neuroleptic malignant syndrome

Neuroleptic Malignant Syndrome (NMS) is an uncommon but serious complication of treatment with neuroleptics characterised by fluctuating disturbances of consciousness together with hyperthermia, muscular rigidity, autonomic instability and rhabdomyolysis (breakdown of muscle tissue). The syndrome usually occurs when patients are first exposed to neuroleptic agents or following a dose change, and seems to be more frequent with agents possessing greater affinity for D2 receptors, although it has been reported with a wide variety of neuroleptics including atypicals (Johnson & Bruxner, 1998; Samia & Buckley, 1998; Thornberg et al., 1993). The syndrome has been postulated to be related to central dopaminergic depletion (Osman & Khuransani, 1995, Takahashi et al., 1996), although there is little direct empirical evidence. One *in vivo* study showed a reduction of striatal D2 receptor binding in the acute stage of NMS, which later recovered to almost normal levels (Jauss et al., 1996).

3.   Dementia with Lewy bodies, Parkinson's disease and neuroleptic sensitivity

Dementia with Lewy bodies (DLB) is a common neurodegenerative dementia, which mainly occurs in late life (McKeith et al., 1996). The main clinical symptoms include visual hallucinations, parkinsonism and disturbances of consciousness, in the context of a global cognitive dysfunction with prominent

attentional dysfunction (Ballard et al., 1999, 2000, see also Chapter 16). Neuropathologically and neurochemically these patients are characterised by cortical as well as brainstem Lewy bodies with neuron loss in the substantia nigra to a lesser extent than in Parkinson's disease (PD) with associated dopaminergic deficits (Piggott et al., 1998). AD pathology is present in most cases of DLB, including β amyloidosis, plaques and neurofibrillary tangles, the latter at about one tenth of the density in DLB compared to AD. Depletion of acetylcholine also occurs which is even more extensive in DLB than AD. As these patients experience severe disturbances of consciousness that are more sustained than seen in other conditions, it is likely that these deficits are explained by the unique profile of neurochemical and neuroanatomical deficits. The majority of clinico-pathological studies indicate cholinergic dysfunction as the main substrate of disturbances of consciousness (Chapter 16, and Perry et al., 1998). In preliminary studies of cortical areas, there is no evidence so far that dopaminergic parameters are associated with the severity of disturbed consciousness (Table 1), although the pre-frontal cortex and basal ganglia have not yet been examined.

Patients with Parkinson's disease have severe loss of nigrostriatal dopaminergic neurons (see also Chapter 15), and may also have mesocortical dopaminergic loss, shown by *in vivo* imaging (Ouchi et al., 1999, Kuikka et al., 1993). PD patients are also affected by neocortical cholinergic deficits, which are greater as cognitive abilities decline, as indicated by loss of the vesicular acetylcholine transporter *in vivo* (Kuhl et al., 1996) and by acetylcholinesterase loss *in vitro* (Lange et al., 1993). Choline acetyltransferase is reported to be unchanged in striatum in PD (Lange et al., 1993; Piggott & Marshall, 1996), but there may be post-synaptic cholinergic deficits in the striatum in PD with dementia, where a reduction in striatal M1 receptor binding is evident (Piggott et al., in preparation). It appears that the effects of dopaminergic loss are counterbalanced to some extent by the level of cholinergic function, and vice versa. For example, treatment with anticholinergic agents improves motor function and hallucinations can be induced by the administration of either anticholinergic agents or L-Dopa.

Important functional interactions of the dopaminergic and other key neurochemical systems have also been demonstrated. Durkin et al., (1986) reported that dopamine in the septum inhibits acetylcholine release in the hippocampus, whilst destruction of the A-10 septal dopaminergic pathways in mice results in increased choline acetyltransferase (Yanai et al., 1993). Pharmacological reduction of nigral dopamine levels to 5% of normal in guinea pigs results in a marked increase (over 70%) in the spontaneous release of acetyl-

Table 1. Dopaminergic activities in orbitofrontal cortex in dementia with Lewy bodies

Dopamine transporter	Ba 11		Ba 12	
Control	18.9±4.73		18.03±8.42	
DLB	25.38±6.04**		24.53±7.48	
D1 receptor	outer	inner	outer	inner
Control	6.66±2.19	7.98±1.78	7.77±1.66	7.85±1.99
DLB	8.21±2.57	7.7±2.41	8.13±2.31	8.02±1.79
D2 receptor				
Control	0.36±0.12		0.36 ±0.11	
DLB	0.36±0.14		0.36 ±0.16	

Temporal Cortex

Dopamine transporter	Ba 20		Ba 21		Ba 22	
Control	46.0±15.0		51.9±4.0		55.6±2.0	
DLB	53.7±13.1		51.6±9.7		51.8±10.7	
D1 receptor	outer	inner	outer	inner	outer	inner
Control	4.79±1.12	3.98±1.75	4.36±2.0	3.29±2.33	4.89±1.35	5.21±1.88
DLB	4.7±2.39	4.2±2.12	6.05±1.32	4.79±1.35	5.87±1.98	5.45±1.58
D2 receptor						
Control	0.6±0.22	0.57±0.19	0.61±0.13	0.76±0.2	0.5±0.04	0.59±0.1
DLB	0.38±0.17*	0.38±0.14*	0.33±0.08**	0.36±0.1**	0.27±0.1***	0.31±0.13*

Results are fmol/mg tissue, mean $\pm$ SD in autopsy brain $*p < 0.05$, $**p < 0.01$, $***p < 0.001$
Ba – Brodmann areas

cholinesterase (Dally & Greenfield, 1994). In addition, within the caudate and putamen, many afferents including dopaminergic terminals carry nicotinic receptors (Martin-Ruiz et al., 1999), which are decreased as a result of the loss of dopaminergic neurons and altered dopamine metabolism in remaining neurons. In neocortical areas including the prefrontal cortex there is evidence that some dopaminergic terminals are opposed to dendrites immunoreactive for gamma-amino butyric acid (GABA) (Erickson et al., 2000).

A similar syndrome to NMS has also been described in DLB patients, where as in NMS, disturbance of consciousness is a core feature. Other characteristics include rigidity and autonomic dysfunction. Mortality rates are high and survivors often experience an irreversible step of cognitive decline (McKeith et al., 1992). Unlike NMS which is rare, this neuroleptic sensitivity syndrome is common in DLB patients exposed to neuroleptic agents—occurring in 25–50% of people prescribed these drugs (McKeith et al., 1992; Ballard et al., 1998). A

similar mechanism probably underlies the two conditions, but DLB patients may be particularly vulnerable because of their unique profile of neurochemical deficits. Piggott et al., (1998) reported an association between severe neuroleptic sensitivity reactions and failure of D2 receptor up-regulation in the striatum, although there was no association with nigral neuron density and the syndrome. This study provides the first clear evidence of a dopaminergic mechanism for these neuroleptic sensitivity reactions, and perhaps explains the particular sensitivity of DLB patients to these syndromes. It does not however explain why patients with equivalent or greater dopaminergic loss, such as those with Parkinson's disease, do not have the same vulnerability, unless the capacity for up-regulation of D2 receptors is retained in Parkinson's disease. In addition, it is unlikely that the failure of D2 up-regulation in the striatum results in the disturbances of consciousness occurring as part of the syndrome, although it is possible that similar problems of up-regulation in the thalamus, hippocampus or pre-frontal cortex may offer a possible explanation. Cortical dopamine D2 receptors are reduced compared to normal elderly controls in temporal cortex (Figure 1 and Table 2) (Piggott et al., unpublished data). Further work to examine these other target areas, and to examine the interactions between the dopaminergic and other neurotransmitter systems may be informative.

Table 2. A preliminary evaluation of the relationship between dopaminergic function and impaired consciousness in dementia with Lewy bodies.

Orbitofrontal or Temporal Cortex Brodmann Area (Ba)	Disturbances of Consciousness (N = 14)	No Disturbances of Consciousness (N = 4)	Statistical Evaluation
D1 Receptors, visualised by [³H] SCH23390 binding			
Ba 11	8.4±2.1	8.8±1.9	$T = 0.35$ $P = 0.73$
Ba 12	8.3±2.1	8.4±1.1	$T = 0.1$ $P = 0.92$
Ba 47	7.1±1.6	8.0±1.1	$T = 1.07$ $P = 0.3$
D2 Receptors, visualised by [¹²⁵I] epidepride binding			
BA 21	0.39±0.085	0.32±0.046	$T = 1.3$ $P = 0.23$
BA 22	0.35±0.12	0.35±0.087	$T = 0.01$ $P = 0.99$
Entorhinal Cortex	0.49±0.18	0.52±0.19	$T = 0.29$ $P = 0.78$
Dopamine Transporter, visualised by [³H] mazindol binding			
BA 11	23.9±3.1	20.8±8.2	$T = 1.0$ $P = 0.33$
BA 12	22.6±6.3	21.5±2.2	$T = 0.3$ $P = 0.78$
BA 47	16.7±4.7	16.3±2.6	$T = 0.1$ $P = 0.89$

Impaired consciousness is rated according to the Clinician Assessment of Fluctuation
Values are fmol/mg tissue, specific binding, mean±standard deviation, in autopsy brain
Ba – Brodmann areas
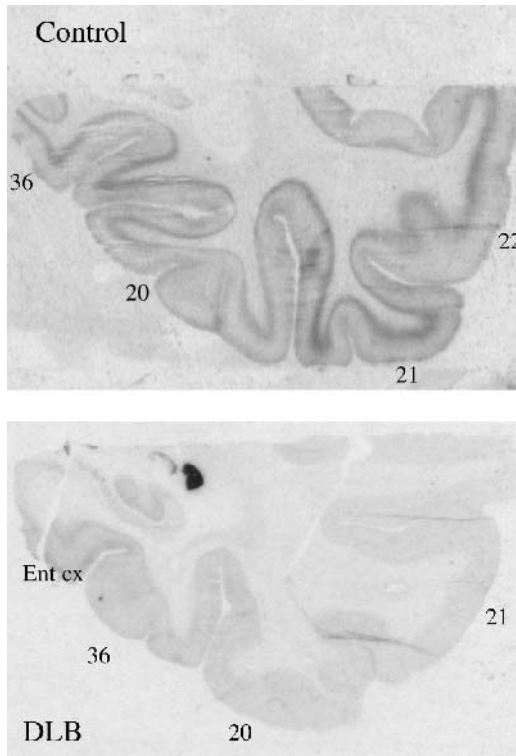
Figure 1. Dopamine D2 receptor binding in human temporal cortex from a patient with dementia with Lewy bodies and matched control. Numbers refer to cortical Brodmann areas and Ent cx = entorhinal cortex.

4.   Cognition and antipsychotic drugs

Because of the difficulties in interpreting the effects upon cognitive performance of antipsychotics with a complex pharmacology, this section focuses on haloperidol, a widely prescribed neuroleptic agent with a major D2 blocking effect. The generally detrimental effects of neuroleptic agents, including haloperidol, on cognition in normal volunteers are well documented (e.g. Beuzen et al., 1999). More rigorous studies have indicated impairments on a range of cognitive domains including error monitoring and working memory, as well as attentional performance on choice reaction time and vigilance tasks (Ramaekers et al., 1999). The impact upon attention, with a mean 50% deterioration of performance in Ramaekers study, is particularly interesting in patients

with dementia since there is a close parallel between attentional performance and consciousness (Walker et al., 2000).

4.1 Experimental animal models

Although results are variable, executive dysfunction and some of the attentional impairments are influenced in animal models by direct manipulation of dopaminergic receptors using pre-frontal infusions (Granon et al., 2000). A D2 receptor antagonist did not influence attentional performance, whereas a D1 receptor agonist improved reaction time and choice reaction time, an effect that was blocked by a D1 receptor antagonist (Granon et al., 2000). Manipulation of the dopaminergic system in the basal ganglia did not however have the same impact (Collins et al., 2000). This finding indicates that the drug effects may not be mediated by ascending dopaminergic pathways. In a further study of the impact of D2 agonists and antagonists on cortical arousal in conscious rats, D2 antagonists increased the mean spectral activity of EEG recordings. D2 agonists at low dose also increased the level of mean spectral activity, but had the reverse effect at higher doses that were sufficient to increase the activation of post-synaptic D2 receptors (Sebban et al., 1999).

Rodent models thus provide opportunities to explore the relationship between dopaminergic function, attention and consciousness. Based upon the well designed study of Granon et al. (2000) showing a clear improvement of attentional performance after the infusion of a D1 agonist into the prefrontal cortex, further study of cortical arousal and variability of reaction times in these models may provide important information. The preliminary data indicating that D2 receptor antagonists may increase cortical arousal (Sebban et al., 1999) is contrary to expectation and requires confirmation

5. Dopamine and consciousness: Other pharmacological insights

A number of additional circumstantial strands of evidence, largely from preliminary experimental studies with animal models, case reports or small case series, indicate a possible link between dopaminergic systems and consciousness. In an animal head injury model of disturbed consciousness, the impact of monterilin hydrate (a novel TRH analog) in improving conscious level was antagonized by a D1 blocking agent (but not by prazosin or scopolamine) (Mushiroi et al., 1996). In a rat model the anaesthetic agent halothane increased the firing of dopaminergic neurons in the substantia nigra and in-

creased the release of striatal dopamine (Fink-Jensen et al., 1994). The clinical literature includes several reports indicating that amantadine (which both increases dopamine release and has NMDA antagonistic properties) can increase conscious level (Zafonte et al., 1998; Kornhuber et al., 1993). Included is a rather unusual case report describing a remarkable near-restitution of consciousness after amantadine administration in a comatose patient with a persistent vegetative state related to "traumatic parkinsonism" following a traumatic brain stem injury (Matsuda et al., 1999).

These observations, in combination with the experimental animal literature indicate a rather complex relationship, where agents which act upon various subtypes of dopaminergic receptors in different brain areas may have divergent impacts upon consciousness, and opposing effects may be seen at different dose thresholds.

6. Summary

The evidence linking neuroleptic exposure to altered consciousness relies mainly on the occurrence of disturbed consciousness as one of the key symptoms of NMS and severe neuroleptic sensitivity reactions. These conditions appear to be precipitated by dopaminergic blockade. A series of case reports indicating the benefits of dopaminergic enhancement in comatose patients is also consistent with a dopaminergic mechanism of consciousness. Preliminary data from experimental animal models is supportive in indicating the potential of agents which act upon D1 and D2 receptors in the prefrontal cortex to alter attentional performance and cortical arousal. Although not conclusive in indicating a major role of dopamine, there is nevertheless accumulating evidence of an important role for dopaminergic transmission in modulating the nature of consciousness, which may relate in particular to the emotional tone and perhaps also time course of conscious awareness.

References

Argenta, G. et al. (1971). *Rivista di Neurologia* 41, 112–118.

Ashton, H. (1987). *Brain systems, disorders and psychotrophic drugs.* Oxford, Oxford University Press.

Ballard, C. et al. (1998). *Lancet* 351, 1032–1033.

Ballard, C. et al. *Archives of Neurology*, (in Press).

Ballard, C. et al. (1999). *American Journal of Psychiatry* 156, 1039–1045.

Beuzen, J.N. et al. (1999). *Journal of Psychopharmacology* 13, 152–158.

Carroll, B.T. & R.E. Taylor (1997). *Journal of Clinical Psychopharmacology* 17, 235–236.

Castillo, E. et al. (1989). *American Journal of Psychiatry* 146, 324–328.

Cherin, P. et al. (1993). *Revue de Medecine Interne* 14, 952–957.

Cohen, J.D. & D.A. Servan-Schreiber (1993). *Schizophrenia Bulletin* 19, 85–104.

Collins, P. et al. (2000). *Behavioral Neuroscience* 114, 3–17.

Dally, J.J. & S.A. Greenfield (1994). *Neurochemistry International* 25, 339–344.

Durkin, T. et al. (1986). *Brain Research* 376, 420–424.

Erickson, S.L. et al. (2000). *Synapse* 36, 47–56.

Fink-Jensen, A. et al. (1994). *Naunyn-Schmiiededbergs Archives of Pharmacology* 350, 239–244.

Granon, S. et al. (2000). *Journal of Neuroscience* 20, 1208–1215.

Jauss, M. et al. (1996). *Movement Disorder* 11, 726–728.

Johnson, V. & G. Bruxner (1998). *Australian and New Zealand Journal of Psychiatry* 32, 884–886.

Kornhuber, J. et al. (1993). *Journal of Neural Transmission – Parkinsons Disease and Dementia Section* 6, 63–72.

Kuhl, D.E. et al. (1996). *Annals of Neurology* 40, 399–410.

Kuikka, J.T. et al. (1993). *European Journal of Nuclear Medicine* 20, 783–786.

Lange, K.W. et al. (1993). *Journal of Neurochemistry* 60, 197–203.

Lidow, M.S. & P.S. Goldman-Rakic (1994). *Proceedings of the National Academy of Sciences* 91, 4353–4356.

McKeith, I. et al. (1992). *British Medical Journal* 305, 673–678.

McKeith, I.G. et al. (1996). *Neurology* 47, 1113–1124.

Martin-Ruiz, C.M. et al. (1999). *Journal of Neurochemistry* 73, 1635–1640.

Mushiroi, T. et al. (1996). *Nippon Yakurigaku Zasshi – Folia Pharmalogica Japonica* 107, 237–245.

Matsuda, W. et al. (1999). *Brain & Nerve* 51, 1071–1074.

Osman, A.A. & M.H. Khurasani (1994). *British Journal of Psychiatry* 165, 548–550.

Ouchi, Y. et al. (1999). *Annals of Neurology* 45, 601–610.

Perry, E.K. et al. (1994). *Neuroreport* 5, 747–749.

Perry, E. et al. (1999). *Trends in Neurosciences* 22, 273–280.

Piggott, M.A. & E.F. Marshall (1996). In R.H. Perry, I.G. McKeith and E.K. Perry (Eds.), *Dementia with Lewy bodies: Clinical, pathological, and treatment issues* (449–467). Cambridge: Cambridge University Press.

Piggott, M.A. et al. (1998). *Biological Psychiatry* 44, 765–774.

Ramaekers, J.G. et al. (1999). *Journal of Clinical Psychopharmacology* 19, 209–221.

Rodriguez-Puertas, R. et al. (1994). *Brain Research* 636, 329–332.

Sacks, O. (1990). *Awakenings.* London, Pan.

Samia, H. & P. Buckley (1998). *American Journal of Psychiatry* 155, 1113–1116.

Scharbach H. *Encaphale* 4, 162–163.

Sebban, C. et al. (1999). *British Journal of Pharmacology* 128, 1045–1054.

Takahashi, A. et al. (1996). *Nippon Rinsho – Japanese Journal of Clinical Medicine* 54, 839–844.

Thornberg, S.A. & L. Ereshefsky (1993). *Pharmacotherapy* 13, 510–514.

Tune, L.E. et al. (1991). *Psychiatric Clinics of North America* 14, 353–373.

Walker, M.P. et al. (2000). *Neurology* 54, 1616–1625.

Walter, C.J. et al. (1972). *British Journal of Psychiatry* 120, 651–662.

Weinberger, D.R. & B. Gallhofer (1997). *International Clinical Psychopharmacology*, 12 suppl. 4, S29–S36.

Yanai, J. et al. (1993). *Neuropharmacology* 32, 113–117.

Zafonte, R.D. et al. (1998). *Brain Injury* 12, 617–621.

Delirium and hallucinations

Heather Ashton

1.   Introduction

The state of conscious awareness, with orientation of self in time and space, depends on finely tuned and accurately co-ordinated activity in multiple neuronal networks in the brain (Park & Young, 1994). Such activity involves parallel processing in many cortical and subcortical pathways including arousal and memory systems (Chapters 3 and 4) and systems involved in mood (Chapters 5 and 18) and utilises an orchestra of many neurotransmitters. The whole ensemble appears to be synchronised by high frequency (40+ Hz) oscillatory electrical activity which binds the component parts together (Llinas et al., 1998; Tallon-Baudry & Bertrand, 1999).

As long as adequate oxygen and nutrients are available, brain functions subserving consciousness are remarkably resistant to disruption by drugs—perhaps because of multiple back-up neurotransmitter systems for each function (Ashton, 1992a) as well as widely distributed overlapping neural networks. However, under certain conditions drugs may disturb this fine balance of activity, producing temporary distortion of conscious thought and awareness manifested in delirium and hallucinations. Some of these drugs and the possible mechanisms by which they produce these effects are described in this chapter.

2.   Delirium

2.1 Definition

Delirium is characterised by a reduction (clouding) in the level of conscious awareness, manifested as disorientation in time and space, or both. Fluctua-

tion between lucidity and clouding, perplexity, patchy amnesia and noisy restlessness, particularly at night, may be evident. Mood is characteristically labile, changing between apathy, excitement, anxiety, depression and hostility. Auditory but more often visual hallucinations in the form of grotesque faces, recognisable figures, or animals may occur. Behaviour disturbances, often based on paranoid ideation, include wandering, escape attempts and aggressive outbursts.

Lipowski (1975) distinguished between hyperactive and hypoactive delirium. The hyperactive form is marked by psychomotor overactivity, excitability, high behavioural and autonomic arousal and a tendency to hallucinations and persecutory delusions. In hypoactive delirium there is reduced psychomotor activity even to the point of stupor, with apathy, daytime somnolence, slowed and impoverished thought processes, and less likelihood of hallucinations. The two clinical variants were regarded as opposite poles of a continuum with mixed forms in between. The common feature is a temporary and often fluctuating incoordination of cortical activity so that brain functions become globally confused, disorganised and chaotic.

2.2 Drug-induced delirium

Delirium is the most commonly encountered psychiatric effect of drug overdose but may occur at usual therapeutic dosage. It may result from direct toxic effects of a drug on cerebral function or from indirect effects on cerebral metabolism, for example hypoglycaemia with insulin or electrolyte disturbance with diuretics. The risk of drug-induced delirium is greatly increased by the presence of underlying cerebral dysfunction such as hepatic encephalopathy, head injury, viral encephalitis, hypoxia, or Lewy body dementia (Chapter 14) and in elderly patients. Some drugs that may cause delirium are shown in Table 1; not all of them are discussed in detail here.

2.2.1 Anticholinergic drugs
Drugs with anticholinergic (antimuscarinic) properties are the pharmacological group that most commonly induce delirium. The effect is dose-related though it may occur in therapeutic situations. The "central anticholinergic syndrome" (Longo, 1966) includes excitement, sometimes preceded by sedation, with hallucinations (usually visual), ataxia and dysarthria and characteristic systemic features of dry mouth, hot dry skin, dilated pupils and tachycardia. The patient is usually restless, continuously plucking at the bedclothes and muttering to some relative who is not present. There may be jerky, semi-

purposive movements of the head, eyes, limbs and trunk as if the patient is constantly being distracted by events in the environment, each competing for attention. There is usually complete amnesia for these events which may persist uninterrupted by sleep for two or three days, although occasionally there is complete recall on recovery.

A variety of anticholinergic drugs with antimuscarinic actions can cause this mainly hyperactive delirium. These include specific antimuscarinics, antipsychotics, antihistamines and antidepressants with anticholinergic actions. Even mydriatic eye drops containing atropine, homatropine, or hyoscine have caused delirium accompanied by hallucinations and subsequent amnesia (Ashton & Young, 1998). Anticholinergic drugs used for treating Parkinsonism (benzhexol, procyclidine and others) can induce hyperactive delirium with visual hallucinations in therapeutic doses and may also cause delirium when abused recreationally (Ashton & Young, 1998). Many phenothiazines and antidepressants have significant anticholinergic effects and can cause hyperactive or hypoactive delirium (Ashton & Young, 1998).

Delirium due to anticholinergic drugs can be rapidly and specifically reversed by anticholinesterase drugs such as physostigmine which inhibit the breakdown of acetylcholine. This action attests to the importance of cholinergic mechanisms in the maintenance of arousal, memory, cognition and conscious awareness (Perry et al., 1999). The cholinergic pathways involved probably include most of those described in Chapter 2 and discussed by Perry et al. (1999) (Fig. 2, Chapter 2). The changes in arousal presumably reflect anticholinergic effects in the pathways from reticular nuclei and thalamus to cerebral cortex which are necessary for general arousal and selective attention (Chapter 3). The amnesia prominent in the central anticholinergic syndrome indicates hypofunction in temporal lobe and hippocampal systems, and the visual hallucinations may be due to effects on muscarinic receptors in visual pathways (Chapter 12).

Most of the anticholinergic drugs which cause delirium have prominently antimuscarinic actions. However, nicotinic receptors are also present in the brain. Mecamylamine, a nicotinic receptor antagonist which penetrates the brain to some extent, has produced delirium (Paykel et al., 1982). Furthermore, general (inhalational) anaesthetics, which by definition decrease arousal, target nicotinic receptors among others (Chapter 9). Conversely, nicotine itself increases arousal and selective attention (Ashton, 1992b).

2.2.2   *Dopaminergic and sympathomimetic drugs*

Both amphetamine and cocaine, which increase synaptic dopamine release and block its reuptake, can cause delirium. "Drug smugglers delirium" has occurred in couriers when the contents of packages of cocaine, secreted in the rectum or vagina, have accidentally leaked out (Ramnaka & Barton, 1993). The delirium is of the hyperactive type with agitation, excitement, aggression, hallucinations and paranoid delusions. Hyperactive delirium may also be caused by levodopa and other dopaminergic drugs used in the treatment of Parkinson's disease (Chapter 13). The effect is dose-related and is more common in patients with dementia (Ashton & Young, 1998). Hollister (1986) points out that dopaminergic drugs are often used with anticholinergic drugs in Parkinson's disease; the combination may add to the risk of delirium.

Amphetamine and cocaine also increase noradrenaline release and a number of drugs with mainly noradrenergic actions can also cause a hyperactive delirium. These include ephedrine, phenylpropanolamine, aminophylline, maprotiline and monoamine oxidase inhibitors (Hollister, 1986).

The delirium caused by these drugs is no doubt partly due to extreme overarousal mediated by central catecholaminergic systems causing an imbalance between monoaminergic and cholinergic activity (Perry et al., 1990; Perry & Perry, 1995). In some cases it can be alleviated by neuroleptics or by benzodiazepines. Exactly why increased catecholaminergic activity should cause hallucinations and paranoid delusions is not clear, but it may be of note that similar symptoms are seen in mania and schizophrenia in which dopaminergic overactivity is implicated (Chapter 15). Shaner (1999) suggests that excessive dopaminergic activation may cause chaotic firing rates in mesolimbic reward pathways (Chapter 5) which could produce distorted thinking, especially paranoid delusions. Dopamine also interacts with cholinergic systems: stimulation of D2 receptors decreases while stimulation of D1 receptors increases acetyl choline release (Trzepacz, 2000).

2.2.3   *Serotonergic drugs*

Serious toxic reactions with delirium can arise when specific serotonin reuptake inhibitors (SSRIs) are taken with other drugs that increase central and peripheral serotonergic activity. Known as the "serotonin syndrome", this reaction consists of excitation, restlessness, fluctuations in consciousness, with tremor, rigidity, myoclonus, sweating, flushing, pyrexia, cardiovascular changes, and rarely coma and death (Sternbach, 1991). The syndrome has occurred when SSRIs have been combined with irreversible monoamine oxidase

inhibitors, lithium, l-tryptophan or occasionally tricyclic antidepressants, all of which have central serotonergic actions.

The mechanisms by which increased serotonergic activity produces delirium are not clear but are probably multiple. The raphe nuclei are closely involved in arousal and increased activity here stimulates activity in the locus coeruleus and may increase transmission through afferent collaterals to the reticular activating system. These effects would not only increase general arousal, causing excitation and perhaps hyperactive delirium, but would also enhance the effects of sensory stimulation, possibly leading to hallucinations. In addition, agonists of 5-HT$_2$ receptors, such as lysergic acid diethylamide (LSD), produce hallucinations, possibly by actions in the temporal and prefrontal cortex (Sadzot et al., 1989). Thirdly, serotonin modulates cholinergic activity, inhibiting release from some areas, while increasing release from others (Trzepacz, 2000), an effect which could cause fluctuations in consciousness.

2.2.4 Alcohol

Delirious states, either hyper- or hypoactive, can occur during acute alcohol intoxication and with increasing doses lead to coma. However, the best known of all delirious states is the delirium of alcohol withdrawal, delirium tremens. The clinical manifestations of this potentially fatal condition are described by Hall & Zador (1997), among others. The onset is usually delayed for 2–3 days after cessation of drinking in alcohol-dependent individuals. It often follows a period of increasing tremulousness, anxiety, hallucinations, autonomic symptoms and sometimes seizures. The full blown clinical picture, which may last hours or days, is characterised by gross tremors, agitation, paranoia, visual, tactile and sometimes auditory hallucinations, illusions, vacillating levels of consciousness, and signs of pronounced autonomic hyperactivity.

The mechanisms of delirium tremens are complex and there is evidence that many neurotransmitter systems are involved. Chronic alcohol use causes down-regulation of (inhibitory) GABA$_A$ receptors and up-regulation of (excitatory) glutamate NMDA receptors (Nutt, 1996). Exposure of these changes on alcohol withdrawal probably accounts for the generalised central nervous system and autonomic overactivity. Decreased GABA and increased glutamate activity could cause convulsions, and a hyperadrenergic state, combined with cholinergic imbalance, is thought to account for anxiety, tremor, sweating and hypertension (Nutt, 1996). These changes may be partially reversed by benzodiazepines (GABA$_A$ receptor agonists) which are the standard treatment for the alcohol withdrawal syndrome. The anticholinesterase physostigmine has also been used successfully in the management of selected cases of delirium

tremens, indicating that cholinergic underactivity is involved (Powers et al., 1991). In addition, there is evidence that alcohol interacts with endogenous opioid systems and a deficiency in endogenous opioid concentrations may contribute to the withdrawal syndrome (Schultz et al., 1980). Delirium tremens also appears to be associated with increased dopaminergic activity since it responds to dopamine receptor antagonists such as haloperidol. Changes in serotonergic activity and related neuroendocrine effects may be further contributory factors (Van der Mast & Fekkes, 2000; Flacker & Lipsitz, 2000) and activation of the cholecystokinin CCK B-receptor may contribute to the anxiety (Nutt, 1996). Added to all these factors, the susceptibility to delirium may be increased in alcoholic subjects by brain and liver damage, malnutrition, dehydration, electrolyte imbalance and increasing age.

2.2.5   *Hypnotics, anxiolytics and anticonvulsants*

Barbiturates, chlormethiazole, benzodiazepines, zopiclone, zolpidem and some anticonvulsants (Table 1) can all cause hypoactive delirium in high doses, sometimes preceded by a hyperactive phase similar to alcohol intoxication. Of the benzodiazepines, potent short-acting compounds such as triazolam and alprazolam are more likely to produce delirium. In elderly subjects therapeutic doses can induce delirium which may lead to bizarre behaviour, falls and fractures (Ashton & Young, 1998). Withdrawal reactions of sedatives and hypnotics include a syndrome with all the characteristics of delirium tremens, except that the tremor is usually less pronounced. The mechanisms involved are probably similar to those of delirium tremens resulting from actions on $GABA_A$ receptors with accompanying changes in glutaminergic activity.

2.2.6   *Phencyclidine, ketamine*

Phencyclidine and ketamine can cause a strange combination of psychiatric symptoms: stimulant and sedative, psychotomimetic and catatonic. Phencyclidine was introduced as an anaesthetic agent which produced an unusual type of dissociative anaesthesia in which patients were unresponsive, analgesic and amnesic for surgery. However, a high risk of unpredictable side effects including dysphoria, confusion, delirium and psychosis precluded its general use and in 1965 it was relegated to veterinary use until 1978 when it was withdrawn in the U.S. Nevertheless, it was widely used as a recreational drug ("Angel Dust") in the mid-seventies and is still used illicitly to some extent, usually in a polydrug context (Gorelick & Balster, 1995). Ketamine, which is chemically and pharmacologically similar, was introduced instead and has a lower incidence of side-effects in anaesthetic practice. However,

Table 1. Some drugs that may cause delirium

Anticholinergic drugs	–	atropine, hyoscine, scopolamine, antiparkinsonian drugs, antipsychotic drugs, antihistamines, antidepressants
Sympathomimetic drugs	–	amphetamines and related compounds, theophylline
Dopaminergic drugs	–	cocaine, levodopa, bromocripine, amantadine
Serotonergic drugs	–	antidepressants: maprotiline, monoamine oxidase inhibitors, drug combinations with specific serotonin reuptake inhibitors causing the 'serotonin syndrome'
	–	lithium, LSD, MDMA
Drugs acting on GABA/glutamate	–	hypnotics/anxiolytics: barbiturates, benzodiazepines, chlormethiazole, chloral derivatives, baclofen
	–	anticonvulsants: phenobarbitone, primidone, phenytoin, sodium, valproate, carbamazepine
	–	alcohol, phencyclidine, ketamine
Drugs acting on opioid systems	–	morphine, pethidine, heroin and others
Corticosteroids	–	prednisone, hydrocortisone, prednisolone also: nonsteroidal anti- inflammatory drugs, aspirin
Antihistamines	–	cimetidine, ranitidine
Cardiovascular drugs	–	digitalis preparations, beta adrenoceptor antagonists, some antiarrhythmic drugs
Drug withdrawal reactions	–	tricyclic antidepressants, monoamine oxidase inhibitors, benzodiazepines, barbiturates, alcohol, opioids.
Drugs used recreationally	–	LSD, MDMA, phencyclidine, ketamine, cannabis, volatile solvents, opioids, cocaine, amphetamines, benzodiazepines, anticholinergics.

(For full references see Ashton & Young, 1998)

recreational abuse of ketamine ("Super-K") is now increasing, often in tablets mixed with ephedrine, selegiline or procaine designed to mimic ecstasy tablets (Shewan & King, 1996).

Acute phencyclidine intoxication can proceed through stages from stupor to coma with unresponsiveness to pain. Delirium lasting several days is common during recovery from coma and may occur transiently as the final phase of an episode of intoxication (Gorelick & Balster, 1995). Ketamine has similar effects when abused recreationally. When used as an anaesthetic in adults, it

can produce a delirium on emergence from anaesthesia, a complication which depends on the dosage used (Dundee et al., 1970).

The mechanisms of action of phencyclidine and ketamine are complex (Gorelick & Balster, 1995). The drugs are non-competitive antagonists at NMDA receptors, and also bind to associated phencyclidine/sigma opioid receptors. They also have agonist actions at dopamine receptors, complex interactions with both nicotinic and muscarinic acetylcholine receptors and poorly understood interactions with noradrenergic and serotonergic systems. These multiple actions may combine to produce delirium and psychotic reactions.

2.2.7   *Other drugs*

A large variety of other drugs can produce delirium (Table 1). Delirium and other neuropsychiatric effects are relatively common with the antimalarial drug mefloquine, even in healthy subjects, and this drug can produce a central anticholinergic syndrome (Speich & Haller, 1994). The histamine H_2 receptor antagonists cimetidine and ranatidine can also cause delirium and other psychiatric abnormalities which may be related to the involvement of histamine in arousal (Schweizer et al., 1995) and interactions with acetylcholine since cimetidine-induced delirium has been reversed by physostigmine (Jenike & Levy, 1983). In addition, delirium has been associated with a range of drugs which may be administered to severely ill patients in whom cerebral hypoxia, electrolyte disturbance and other general factors may contribute to brain dysfunction (Ashton & Young, 1998).

2.3   Is there a final common neural pathway in delirium?

The heterogeneity of drugs and other causes that can induce delirium has led some authors to suggest that these agents all act through a final common pathway, involving certain brain regions or circuits and certain neurotransmitters. For example, Trzepacz (2000) marshals data from many studies and suggests that the neurotransmitters most implicated in mediating the symptoms of delirium are acetylcholine and dopamine, interacting through pathways in prefrontal cortex, thalamus, fusiform cortex, posterior parietal cortex, and basal ganglia. "Cholinergic deficiency and dopaminergic excess, either absolute and/or relative to each other, is the dominant theory of neurotransmission abnormality that may underlie the final common pathway of delirium" (Trzepacz, 2000). This theory is supported by Tune (2000) who found in clinical studies that the prevalence of delirium was significantly higher in patients

with various medical/surgical conditions who were receiving larger numbers of anticholinergic drugs. However, Van der Mast & Fekkes (2000) stress the importance of serotonin and its amino acid precursor tryptophan in delirium but point out that both excess serotonergic activity (e.g. the serotonin syndrome) and diminished serotonergic function (e.g. alcohol withdrawal delirium) can be associated with delirium.

Some of the many factors that can cause delirium are shown in Figure 1. Some authors (Flacker & Lipsitz, 2000) have concluded that there is probably no final common pathway to delirium, suggesting instead that delirium is the final common *symptom* that can result from aberrations in numerous different transmitter pathways and pathological processes. Since normal brain function, and especially consciousness, depends on accurate communication between a very large number of neurotransmitter systems, the latter conclusion seems more rational. To search for a final common pathway may be to oversimplify
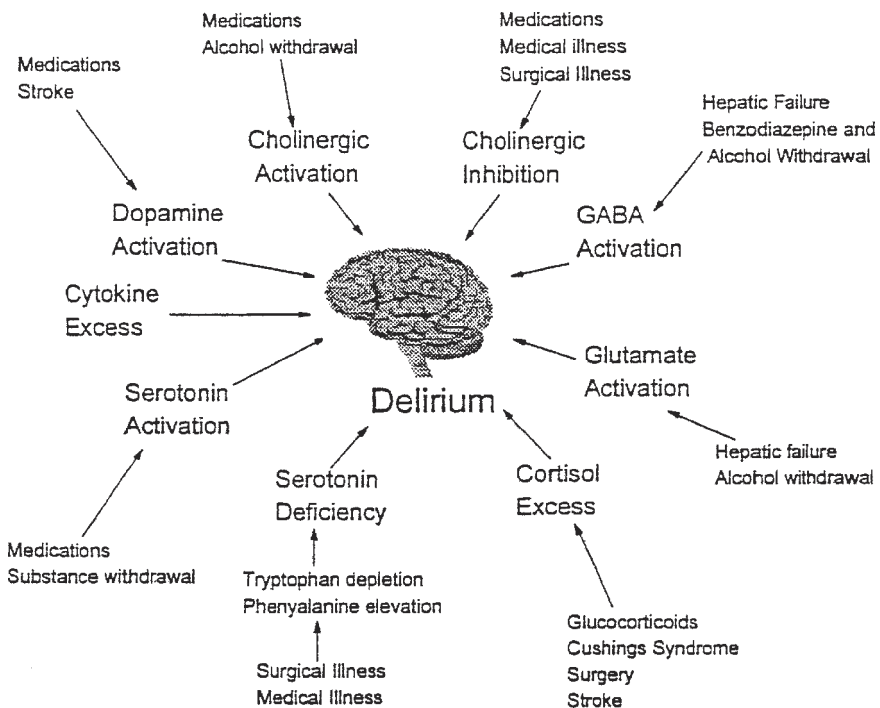
Figure 1. Some factors which may cause delirium.
(From Flacker & Lipsitz, 1999 with permission)

the issue: the brain is far too complex to rely on a single final common pathway or neurotransmitter for any function or dysfunction.

3. Hallucinations

3.1 Definition

Hallucinations are broadly defined as perceptions that occur in the absence of a corresponding external stimulus. Characteristics which help to distinguish them from other abnormal perceptions or sensory distortions include (Sims, 1988): (1) hallucinations are perceived as real, having the full force and impact of a real perception; to the subject they are indistinguishable from real percepts; (2) hallucinations are unwilled, occur spontaneously and intrusively and cannot readily be controlled by the percipient. They may occur in the setting of a clear consciousness in which the subject remains orientated in time and space and is simultaneously able to perceive external stimuli normally. They may also occur in the setting of a disturbed consciousness, as in delirium where they may merge with illusions and misperceptions, or in altered states of consciousness as in temporal lobe epilepsy or in the hypnagogic and hypnopompic hallucinations of sleep. Thus the definition of hallucinations can become blurred, and it is difficult to make a clear separation of hallucinations from such phenomena as illusions, pseudohallucinations, flashbacks and dreams. In all of these cases the sensation seems real to the subject and the sense of self, an essential part of consciousness, is preserved. According to Dennett (1987) distinctions between these phenomena are of little theoretical importance, and they may all involve similar mechanisms. Nevertheless, it seems clear that hallucinations generally originate within the brain—although they may sometimes be prompted by external stimuli, and in some cases (e.g. schizophrenia) are interpreted as originating externally.

Hallucinations can involve any of the senses. They may be visual, auditory, tactile, gustatory, olfactory, kinaesthetic/proprioceptive (sensation of movement, imbalance or vibration), synaesthetic (e.g. auditory stimuli perceived as colours; an auditory perception after a bright light), or extracampine (hallucinations experienced outside the limits of the sensory field, e.g. the feeling that someone is walking behind). They can also consist of distortions of the body image and of size, distance and time; objects can appear abnormally small (micropsia) or large (macropsia); time can seem to pass more quickly or more slowly than real time. Hypnagogic hallucinations, usually visual or auditory,

can occur at the onset of sleep; hypnopompic hallucinations on the edge of awakening. Visual hallucinations may start as unformed images such as abstract shapes or flashes of light, progressing to complex, sometimes grotesque, forms of animals or people and scenes in vivid colours (Barodawala & Mulley, 1997). Some hallucinations merge into illusions or misperceptions, so that a coat hanging on the door takes on the form of a person. Auditory hallucinations may be unformed, grading from tinnitus, hissing, whistles to bangs and thumps but are occasionally musically formed (e.g. singing voices) (Johnson et al., 1993) and are often of voices uttering insults or threats. Gustatory and olfactory hallucinations consist of usually unpleasant tastes or smells which the patient may perceive as coming from his own body. All these types of hallucinations, and also persisting perception disorder (flashbacks), can be caused by drugs.

3.2 Drug-induced hallucinations

Hallucinations can be caused by any of the drugs that induce delirium, described above. Drug-induced hallucinations can also occur in the presence of a clear consciousness and can be caused by a large number and wide variety of drugs (Table 2). To some extent the hallucinations are characteristic of the inducing drug (Table 3) and may reflect perturbations of particular neurotransmitters or brain areas. Only a sample of drug-induced hallucinations are described here.

3.2.1 *Anticholinergic drugs*

Hallucinations with anticholinergic drugs occur in the hyperactive delirium ("central cholinergic syndrome") induced by these drugs either in overdose, or taken for euphoric or hallucinogenic purposes (Chapter 13). The hallucinations are mainly visual taking the form of people, faces, animals, and others. The hallucinations are presumably due to disruption of cholinergic pathways as described for delirium, along with unopposed sympathetic activity as evidenced by tachycardia, dilated pupils and other systemic effects. The predominance of visual hallucinations may be related to the high concentration of muscarinic (M_1, M_3, M_4) receptors in the lateral geniculate nucleus and visual cortex (Chapter 13). Intense visual stimulation, combined with a hyperexcitable state, may also play a part since the pupils are maximally dilated and the power of accommodation is lost.

Table 2. Some drugs that can induce hallucinations (visual, auditory, tactile, and other hallucinations, not necessarily associated with delirium or psychosis)

Analgesics/anaesthetics		
indomethacin, fenbufen	ketamine*	opiates, opioids*
opioid agonists/antagonists* (pentazocine, nalorphine, naloxone, buprenorphine)	nefopam	salicylates
Anticonvulsants		
phenytoin	sodium valproate	ethosuximide
Anticholinergic drugs*		
atropine, hyoscine	atropine, hyoscine, tropicamide, cyclopentolate, eye drops	benztropine, benzhexol orphenadrine, procy-clidine
Antidepressants		
lithium	monoamine oxidase inhibitors	tricyclic antidepressants*
specific serotonin reuptake inhibitors		
Antihistamines*		
cyclizine, dimenhydrate, diphenhydramine, pheniramine		
Antiparkinsonian drugs		
amantadine	bromocriptine	L-dopa
Hypnotics/sedatives/anxiolytics*		
benzodiazepines (high dose or withdrawal)	zopiclone, zolpidem	
Other therapeutic agents		
anabolic steroids*	baclofen (withdrawal)	cimetidine, ranitidine
clonidine	corticosteroids*	oral contraceptives
tacrine(?)		
Recreational drugs*		
alcohol (acute toxicity and withdrawal)	amphetamines and related drugs also used	cannabis
lysergic acid diethylamide (LSD) and related drugs	therapeutically (ephedrine, mephentermine, mazindol,	cocaine
organic solvents	methylphenate, cathine,	N-methyl-d-amphetamine (NMDA) and related drugs
3,4-methylenedioxy methamphetamine (MDMA, Ecstasy)	diethylpropion, fenfluramine)	phencyclidine, ketamine

* Also used as drugs of abuse
(Full references for each drug are given in Ashton & Young, 1998)

Table 3. Types of hallucinations associated with particular drugs*

Type of hallucination	Associated drugs
Visual	
unformed: flashes, shapes, colours	– LSD, MDMA, cannabis
formed: grotesque faces, animals, people	– anticholinergics, alcohol withdrawal, drug induced deliria and psychotic states.
Lilliputian: little people, animals	– alcohol withdrawal
Auditory	
unformed: tinnitus, whistles	– benzodiazepine withdrawal
formed: voices, often insulting or accusatory	– cocaine, amphetamine, alcoholic hallucinosis, drug induced deliria and psychotic states
Tactile	
formication, feeling of insects etc.	– cocaine, amphetamines, alcohol and benzodiazepine withdrawal
Synaesthesia	
merging of senses	– LSD, cannabis
Time distortion	– LSD, cannabis
Space distortion	
macropsia, micropsia, distortion of body image	– LSD, cannabis
Kinaesthesia Feelings of movement, imbalance, Inner vibration	– alcohol, benzodiazepines
Gustatory, olfactory	– benzodiazepine or alcohol withdrawal, drug-induced psychotic states
Hypnagogic, hypnopompic onset and offset of sleep (often associated with nightmares)	– beta-blockers, benzodiazepine withdrawal
Flashbacks	– LSD, cannabis, MDMA, phencyclidine, ketamine

*Most of the drugs can cause most types of hallucinations (see text) but some types of hallucinations are characteristic of certain drugs.

3.2.2   *Dopaminergic and sympathomimetic drugs*

Chronic use of amphetamine or cocaine can give rise to visual, tactile, olfactory and auditory hallucinations (Miller, 1991; Sims, 1988). Formication is characteristic in which the user experiences the sensation of little animals or insects crawling over the body or just under the skin or sees his body covered in sores or vermin. These hallucinations may lead to delusions of infestation.

Auditory hallucinations consist typically of voices making derogatory personal statements may also occur. They are frightening and may prompt aggressive and violent behaviour (O'Brien & Woody, 1994). The hallucinations in these drug-induced states in chronic users occur in an otherwise clear consciousness, but similar hallucinations occur in the delirium which may follow acute intoxication with these drugs or in their withdrawal reactions.

Other drugs related to amphetamines or cocaine may cause similar symptoms (Table 2), and formication is not uncommon in alcohol and benzodiazepine withdrawal (Sims, 1988; Ashton, 1997), both of which are associated with increased catecholamine activity.

3.2.3   *Alcohol*

Tactile, auditory and visual hallucinations commonly occur in delirium tremens (see above). Such visual hallucinations are commonly Lilliputian (miniature people or animals) (Sims, 1988). The patient sees little creatures walking over him and can feel their footsteps and hear them shouting obscene jokes and abusive remarks. The hallucinations are usually terrifying but may also contain comical elements and are mixed with illusions. An account from Dickens' *Pickwick Papers* is quoted by Sims (1988): "There were insects too, hideous crawling things with eyes … The walls and ceiling were alive with reptiles—the vault expanded to an enormous size—frightful figures flitted to and fro—and the faces of men he knew, rendered hideous by gibing and mouthing, peered out from among them …." Such hallucinations, with their evil and sinister undertones, are difficult to distinguish from nightmares which also occur in alcoholic delirium.

Auditory and sometimes visual hallucinations in the setting of a clear consciousness with full orientation and vivid recall can also occur in chronic alcoholic hallucinosis during or after a period of heavy alcohol consumption (Sloane & O'Boyle, 1998). The auditory hallucinations are similar to those of schizophrenia, consisting of threatening or accusatory voices or commands to commit suicide or homicide. They are often accompanied by delusions, especially pathological jealousy, in which the spouse may be falsely accused of sexual indiscretions. Sloan and O'Boyle (1998) describe a case of vivid visual hallucinations in a patient who suddenly stopped drinking after consuming 32 units of alcohol daily for over 25 years. There was no clouding of consciousness, but for 48 hours he saw groups of people on a (non-existent) hotel security monitor. Details were particularly clear and included a blonde lady smoking a cigarette and a black child riding a bicycle.

Hallucinations occurring in both alcoholic hallucinosis and delirium tremens are no doubt associated with abnormalities in several neurotransmitter systems. As described under delirium tremens, they probably involve increased activity of excitatory mechanisms, especially activation of NMDA receptors, and of catechol amines, combined with reduced functioning of GABA, alpha-2 adrenoceptor and serotonergic activity (Sloan & O'Boyle, 1998). These authors suggest that the increase in central dopaminergic activity which follows alcohol cessation is central to the development of hallucinations. Successful treatment of both auditory and visual hallucinations with dopamine antagonists such as haloperidol support the suggestion that the hallucinations reflect a hyperdopaminergic state.

3.2.4   *Hallucinogenic drugs (LSD, MDMA, cannabis)*

Acute psychological reactions to LSD include alterations in mood, distortion of time and space with macropsia and micropsia, depersonalisation, dream-like feelings and visual hallucinations, often of geometric figures. Rarely auditory or tactile hallucinations are experienced. At the same time, there are other perceptual changes including sensory hypersensitivity, and synaesthesia, the merging of different sensory modalities. These effects may be elaborated into a complex visual and emotional experience with mystical qualities so that subjects feel that their thoughts are of great clarity and meaningfulness. Metaphysical preoccupations dominate and there may be a feeling of disembodiment and oneness with the cosmos. A feeling of omnipotence may supervene with irrational beliefs such as belief in the ability to fly (Hollister, 1982).

Dr. Albert Hofmann, the Sandoz chemist who first manufactured LSD along with a colleague W.A. Stoll, described his experiences after taking this drug (cited by Brecher, 1972) … "I lay down and sank into a not unpleasant delirium, which was characterised by extremely excited fantasies. In a semiconscious state with my eyes closed (I felt the daylight to be unpleasantly dazzling), fantastic visions of extraordinary realness and with an intense kaleidoscopic play of colours assaulted me …" On taking the drug for a second time, Hofmann (cited by Brecher, 1972) wrote: "My field of vision swayed before me and was distorted like the reflections in an amusement park mirror. I had the impression of being unable to move … although we had cycled at a great pace … the faces of those around me appeared as grotesque coloured masks … occasionally I felt as if I were out of my body … All objects appeared in unpleasant, constantly changing colours, the predominant shades being green and sickly blue. With closed eyes multihued, metamorphosing fantastic images overwhelmed me. Especially noteworthy was the fact that sounds were

transposed into visual sensations so that from each tone or noise a comparable coloured picture was evoked, changing in form and colour kaleidoscopically."

Aldous Huxley, perhaps with a greater sense of mysticism, described similar experiences with the related drug mescaline, although in his case some of the altered visual perceptions were interpreted as possessing transcendental beauty (Huxley, 1954). It has been argued that the psychological phenomena of LSD, mescaline and related drugs are not true hallucinations since for the most part the LSD user sees what is really there, but sees it in distorted or changing forms. He misinterprets what he sees, but usually remains aware that he is experiencing drug-induced phenomenon (Brecher, 1972).

LSD can also provoke a prolonged psychiatric reaction which includes paranoid delusions, schizophreniform auditory hallucinations and overwhelming panic. This reaction, which closely resembles schizophrenia, occurred in 1–2 per cent of patients administered LSD for psychotherapeutic purposes (Malleson, 1971). Medical use of LSD is now obsolete but similar psychoses are seen in recreational users (Seymour & Smith, 1991).

Ecstasy (MDMA) is chemically related to LSD and some of its psychological effects are similar though not identical (Seymour & Smith, 1991; Green et al., 1995). The most marked psychological effects of MDMA when taken recreationally at dance parties or "raves" in doses of 50–150 mg, are a relatively gentle euphoria, combined with an extraordinary feeling of social empathy and love of others, giving rise to an ecstatic feeling that everything is good and beautiful. At higher doses (250–300 mg) visual disturbances may develop, including hallucinations of shapes and patterns, or objects appearing to be shimmering or moving, along with anxiety and paranoid feelings (Davison & Parrott, 1997). Larger doses (300–400 mg) may cause severe anxiety, panic, paranoid psychosis with grandiose or persecutory delusions and auditory hallucinations, suicidal thoughts and violence. Repeated use can lead to depression and cognitive impairment (Curran & Travill, 1997).

Cannabis, although not chemically related to LSD, can elicit many of the same psychological effects (Paton et al., 1973). A euphoric "high" is accompanied by changes in all sensory modalities. There may be heightened perception of colour and subjects may see patterns of colours, dimming, brightening and flowing. Sounds seem more vivid and musical appreciation is increased. Sensations of floating, weightlessness, heaviness or swelling, hot and cold feelings, numbness and tingling may be experienced. Spatial perception is distorted: objects can seem abnormally small or large, and the surroundings may appear to advance and recede. The perception of time is distorted, so that felt time moves faster than clock time. Feelings of timelessness, or time standing still and blur-

ring of past, present and future may come and go. There may be an experience of deep insight and significance, alternating with sensations of utter futility. With high doses, cannabis can produce delirium or a psychosis with visual and auditory hallucinations, feelings of unreality and depersonalisation. These reactions are becoming more common with the increased use of high potency preparations such as Skunkweed and Netherweed (Wylie et al., 1995).

Other hallucinogenic drugs including substances related to LSD are mentioned under delirium. Phencyclidine and ketamine can also produce similar hallucinatory states without delirium including time distortion, distortion of body image, synaesthesia, visual hallucinations, depersonalisation, derealisation, paranoid ideation and a schizophreniform psychosis which includes the negative symptoms of schizophrenia (Gorelick & Balster, 1995).

The mechanisms by which LSD and MDMA produce hallucinations are probably largely through serotonergic activation, as described for delirium. LSD is a potent agonist of 5-HT$_2$ receptors in the temporal and prefrontal cortex (Sadzot et al., 1989), and has both agonist and antagonist activity at dopaminergic and adrenergic receptors (Freedman & Boggan, 1982). The acute effects of MDMA are probably due to release of serotonin, as well as dopamine (Green & Goodwin, 1996; Green et al., 1995). This may be followed by degeneration of serotonergic neurons and long-term effects such as depression and cognitive impairment (Ricaurte et al., 1990; Curran & Travill,1997).

The psychological effects of cannabis are due to cannabinoids such as Δ^9-tetrahydrocannabinol (THC) which interact with specific cannabinoid receptors in the brain (Devane et al.,1988; Matsuda et al., 1990). The functions of these receptors are not known but high concentrations are present in sensory and limbic areas, and THC also increases dopamine release from the nucleus accumbens and frontal cortex (Tanda et al., 1987) and decreases the release of acetylcholine (Trzepacz, 2000).

3.2.5 *Flashbacks (persisting perception disorder)*
Flashbacks, transient recurrences of some aspects of an hallucinogenic drug experience occurring after a period of normality and no further drug ingestion can occur after use of any of the hallucinogenic drugs mentioned above. They usually consist of perceptual disturbances but can include emotional and somatic reactions. They may occur spontaneously but may be triggered by anxiety, fatigue, stress, environmental context and other drugs. Flashbacks are more common after multiple than single hallucinogen ingestion and may last for several months or continue episodically for over 5 years (Abraham, 1983). They

are perhaps not true hallucinations since the subject is usually (though not always) aware of their abnormal nature.

The LSD flashback includes colour confusion, flashes of bright colour, geometric shapes, halos around objects, positive and negative after-images, macropsia and micropsia, and trailing phenomena (apparent trails following moving objects) (Abraham, 1983). Woody (1970) reported three cases of visual disturbances occurring while driving, increasing the risk of traffic accidents in habitual users of LSD, cannabis and other hallucinogens. Cannabis can cause similar flashbacks, often accompanied by an intense emotional experience (Brill & Nahas, 1984; Paton et al., 1973), and cannabis can trigger flashbacks in LSD users (Abraham, 1983). Unpleasant flashbacks have been described after use of MDMA (McGuire & Fahy, 1992) including contorted and menacing faces as well as visual illusions, and after ketamine (Jansen, 1993).

The mechanisms of flashbacks are probably mixed. Some cases may be similar to post-traumatic stress disorder induced by a "bad trip" (Paton et al., 1973). Abraham (1983) suggested that some of the visual phenomena, such as trailing and after-images, were due to failure of inhibition in visual pathways, possibly mediated in the lateral geniculate nucleus which (in the macaque monkey) contains on-off colour neurons with receptor fields similar to those described in flashbacks. The neurochemical causes of such flashbacks, which can be very disturbing, remains elusive and attempts at treatment are usually ineffective.

3.2.6   *Other drugs*

Many other drugs with diverse modes of action can produce hallucinations (Table 2). For example, beta-adrenergic receptor antagonists can cause nightmares and hypnagogic and hypnopompic hallucinations, probably because of effects on central adrenergic receptors affecting rapid eye movement sleep (REMS) (Ashton & Young, 1998; Chapter 7). By contrast, opioids traditionally cause blissful floating dreams, but morphine and partial opioid agonists/antagonists (pentazocine, buprenorphine) can cause naloxone-reversible visual and auditory hallucinations, which may be due to actions on k-opioid receptors (Connick et al., 1990).

3.3   Mechanisms of hallucinations

3.3.1   *Anatomical sites*

The Canadian neurosurgeon Wilder Penfield was the first to demonstrate that specific hallucinations could be provoked by electrical stimulation of certain

sites in the brain (Penfield & Perot, 1963). For example, a musical melody could be evoked into consciousness by stimulation of particular locations on the lateral aspect of the temporal lobes, and the same melody would recur if stimulation was later repeated at the same site. The advent of non-invasive functional brain imaging techniques have since allowed further exploration of the location and functional correlates of hallucinations (Weiss & Heckers, 1999). The subjects have been alcoholic or schizophrenic patients with mainly verbal auditory hallucinations and patients with schizophrenia or Charles Bonnet syndrome experiencing visual hallucinations, but the results may apply to drug-induced hallucinations in general.

The main finding from all these studies is that hallucinations are associated with modality-specific activation in cerebral areas involved in normal sensory processing. Thus, during auditory hallucinations there is activation of temporal lobe primary and secondary auditory areas (right and left), and also of basal ganglia and hippocampus, with decreased activity in frontal areas. Verbal hallucinations have also been associated with changes in activity in specific language centres (Broca's area) (Cleghorn et al., 1992; McGuire et al., 1993). Increased activity in the affected areas starts shortly before the hallucinations are perceived, and the active areas appear to compete with external stimuli for central processing sites (Woodruff et al., 1997). In a patient with musical hallucinations who was cognitively intact and had normal hearing Kasai et al. (1999) demonstrated increased blood flow in the right superior temporal and inferior frontal gyri (auditory association areas) during the hallucinations.

In the case of visual hallucinations, similar studies have shown that these are correlated with activity in the occipital lobes (Ffytche et al., 1998). The localisation of activity was associated with the specific phenomenological characteristics of the hallucination; for example hallucinations of unfamiliar faces were found by Kanwisher et al. (1997) to be accompanied by increased activity in the left middle fusiform gyrus, an area related to unfamiliar face stimuli. As with auditory hallucinations, increased activity in the affected area preceded the onset of the hallucination.

3.3.2   *Neurochemistry of hallucinations*

The anatomical studies indicate that activation of modality-specific primary and secondary sensory areas and their subcortical connections are involved in different types of hallucinations. The distribution of the neurotransmitter pathways supplying these areas (Figs 2–5, Chapter 1) suggests that many neurotransmitters are involved. This conclusion is supported by the large number and heterogeneity of drugs that can produce hallucinations (Table 2). Thus,

for hallucinations, as for delirium, there is clearly no final common pathway or pre-eminent neurotransmitter.

Hallucinations occurring in delirium tend to occur in the hyperactive form, accompanied by a high level of arousal and at the same time a lowering of vigilance, impairment of perception and reduction of reality monitoring (Dennett, 1987; Bentall & Slade, 1985; Weiss & Heckers, 1999), a prime ingredient of conscious awareness. This central excited state is accompanied by increased monoaminergic and/or excitatory amino acid activity and decreased GABA-ergic activity with a relative or absolute (in the central anticholinergic syndrome) decrease of cholinergic activity. This imbalance between monoaminergic and cholinergic activity is suggested to lead to increased background noise and thus a decrease in neuronal signal to noise ratio (Dennett, 1987; Perry et al., 1990; Perry & Perry, 1995). Excitation of sensory areas may then arise spontaneously or with minimal external stimulation. Sometimes, even though consciousness is impaired, there is apparently an attempt to make sense of the sensory perceptions. For example, a sense of prickling on the skin caused by piloerection due to sympathetic nervous system stimulation is "explained" by visible or invisible crawling insects, and cracks in the walls or ceiling are interpreted as writhing snakes.

Hallucinations occurring in a clear consciousness are perhaps more difficult to explain, but they too arise from a background of neurochemical abnormality (e.g. alcoholic hallucinosis, schizophrenia), in which information flow between different cortical areas is likely to be disrupted. As noted by Park and Young (1995), pruning the connections between units in artificial neural networks can result in bizarre outputs with the development of "parasitic foci" in which groups of neurons become functionally autonomous. These authors suggest that if such a focus arose in the brain areas responsible for speech perception, then auditory hallucinations might be engendered. It is perhaps noteworthy that many of the drugs that produce hallucinations can also produce a schizophreniform psychosis and aggravate positive symptoms in schizophrenic patients. In addition, hallucinogenic drugs which act directly on sensory areas (LSD, cannabis) might set up similar parastic foci. Such phenomena have similarities to the hallucinations and visions of temporal lobe epilepsy, another example of localised autonomous neural discharge.

4. Conclusion

The basis of both hallucinations and delirium appears to be a breakdown in accurate communications between different parts of the brain. Such communications depend on coordinated electrical signals, both excitatory and inhibitory, engendered by a large number of neurotransmitters. Drugs may disrupt the balance of activity between different neurotransmitters that is required to maintain a clear sense of reality.

References

Abraham, H.D. (1983). *Archives of General Psychiatry* 40, 884–889.

Ashton, C.H. (1992a). *Brain Function and Psychotropic Drugs.* Oxford: Oxford University Press.

Ashton, C.H. (1992b). *Journal of Smoking-Related Disorders* 3, 35–41.

Ashton, C.H. (1997). *Journal of the Royal College of Physicians of London* 31, 221–222.

Ashton, C.H. & A.H. Young (1998). In D.M. Davies, R.E. Ferner & H. de Glanville (Eds.), *Davies's Textbook of Averse Drug Reactions* (669–731). London: Chapman & Hall Medical.

Barodawalla, S. & G.P. Mulley (1997). *Journal of the Royal College of Physicians* 31, 42–48.

Bentall, R.P. & P.D. Slade (1985). *British Journal of Clinical Psychology* 24, 159–169.

Brecher, M. (1972). In E.M. Brecher (Ed.), *Licit and Illicit Drugs: The Consumers Union Report on Narcotics, stimulants, depressants, inhalants, hallucinogens & marijuana — including caffeine, nicotine and alcohol* (335–393). Mount Vernon, New York: Consumers Union.

Brill, H. & G.G. Nahas (1984). In G.G. Nahas (Ed.), *Marihuana in Science and Medicine* (263–306). New York: Raven Press.

Cleghorn, J.M. et al. (1992). *American Journal of Psychiatry* 149, 1062–1069.

Connick, J., P. Fox & D. Nicholson (1990). *Trends in Pharmacological Sciences* 11, 274–275.

Curran, H.V. & R.A. Travill (1997). *Addiction* 92, 821–831.

Davison, D. & A.C. Parrott (1997). *Human Psychopharmacology* 12, 221–226.

Dennett, D. (1987). In R.L. Gregory (Ed.), *The Oxford Companion to the Mind.* (299–300). Oxford: Oxford University Press.

Devane, W.A. et al. (1988). *Molecular Pharmacology* 34, 605.

Dundee, J.W. et al. (1970). *Lancet I*, 1370–1371.

Ffytche, D.H. et al. (1998). *Nature Neuroscience* 1, 738–742.

Flacker, J.M. & L.A. Lipsitz, (1999). *Journal of Gerontology A. Biological Sciences Medical Sciences* 54, B239–B246.

Freedman, D.X. & W.O. Boggan. (1982). In F. Hoffmeister & S. Stille (Eds.), *Psychotropic Agents Part III* (57–88). Heidelberg: Springer Verlag.

Gorelick, D.A. & R.L. Balster. (1995). In H.Y. Meltzer (Ed.), *Psychopharmacology: The fourth generation of progress* (1767–1776). New York: Raven Press.

Green, A.R. & G.M. Goodwin, (1996). *British Medical Journal* 312, 1493–1494.

Green, A.R. et al. (1995). *Psychopharmacology* 119, 247–260.

Hall, W & D. Zador. (1997). *Lancet 349*, 1897–1900.

Hollister, L.E. (1982). In F. Hoffmeister & G. Stille (Eds.), *Psychotropic Agents Part III. Alcohol and psychotomimetics, psychotropic effects of central acting drugs.* (321–344). Berlin: Springer Verlag.

Hollister, L.E. (1986). *Medical Toxicology 1*, 428–448.

Huxley, A (1954). *Doors of perception.* London: Flamingo Press.

Jenike, M.A. & J.C. Levy (1983). *Journal of Clinical Psychopharmacology* 3, 43–44.

Jansen, K.L.R. et al. (1993). *British Medical Journal* 306, 601–602.

Johnson, M. et al.(1993). *Acupuncture in Medicine* 11, 98–102.

Kanwisher, N. et al. (1997). *Journal of Neuroscience* 17, 4302–4311.

Kasai, K. et al. (1999). *Lancet* 354, 1703–1704.

Lipowski, Z.J. (1975). *Journal of Nervous and Mental Disorders 145*, 227.

Llinas, R.V. et al. (1998). *Philosophical Transactions of the Royal Society of London B*, 353, 1841–1849.

Longo, V.G. (1966). *Pharmacological Reviews* 18, 965.

Malleson, N. (1971). *British Journal of Psychiatry* 118, 229.

Matsuda, L.A. et al. (1990). *Nature* 346, 561.

McGuire, P. & T. Fahy (1992). *British Journal of Psychiatry* 169, 276.

McGuire, P.K. et al. (1993). *Lancet* 342, 703–706.

Miller, N.S. (1991). In N.S. Miller (Ed.), *Comprehensive Handbook of Drug and Alcohol Abuse* (427–435). New York: Marcel Dekker.

Nutt, D.J. (1996). *Lancet* 347, 31–36.

O'Brien, C.P. & G.E. Woody (1994). In G.G. Nahas & C. Latour (Eds.), *Physiopathology of illicit drugs: Cannabis, cocaine, opiates* (219–232). Oxford: Pergamon Press.

Park, S.B.G. & A.H. Young. (1994). *Philosophy, Psychology & Psychiatry* 1, 51–58.

Paton, W.D.M. et al. (1973). In R. Mechoulam (Ed.), *Marijuana* (335–365). London & New York: Academic Press.

Paykel, E.S. et al. (1982). *Journal of Clinical Psychopharmacology* 2, 14–39.

Penfield W. & P. Perot (1963). *Brain* 86, 595–599.

Perry, E.K. & E. Marshall et al. (1990). *Journal of Neurochemistry* 55, 1454–1456.

Perry, E.K. & R.H. Perry (1995). *Brain Cognition* 28, 140–158.

Perry, E. & M. Walker et al. (1999). *Trends in Neurological Sciences* 22, 273–280.

Powers, J.S.D. et al. (1991). *Journal of Clinical Pharmacology* 21, 57–60.

Ramnakha, P.S. & I. Barton (1993). *British Medical Journal* 306, 470–471.

Ricaurte, G.A., K.T. Finnegan et al. (1990). *Annals of the New York Academy of Sciences* 600, 699–710.

Sadzot, B., J.M. Baraban et al. (1989). *Psychopharmacology* 98, 495–499.

Schultz, R. et al. (1980). *Psychopharmacology* 68, 221–227.

Schweizer, E. et al. (1995). In F.E. Bloom & D.J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress.* (1349–1360). New York: Raven Press.

Seymour, R.B. & D.E. Smith (1991). In N.S. Miller (Ed.), *Comprehensive handbook of drug and alcohol abuse* (455–476). New York: Marcel Dekker Inc.

Shaner, A. (1999). *Medical Hypotheses* 52, 119–123.

Shewan, D. & L.A. King (1996). *British Medical Journal* 313, 424.

Sims, A. (1988). *Symptoms in the Mind: An introduction to descriptive psychopathology* London: Balliere Tindall.

Sloan, D. & J. O'Boyle (1998). *Irish Journal of Psychological Medicine* 15, 35–36.

Speich, R. & A. Haller (1994). *New England Journal of Medicine* 331, 57–58.

Sternbach, H. (1991). *American Journal of Psychiatry* 148, 705.

Tallon-Baudry, C. & O. Bertrand (1999). *Trends in Cognitive Sciences* 3, 151–161.

Tanda, G. et al. (1987). *Science* 276, 2048–2050.

Trzepacz, P.T. (2000). *Seminars in clinical neuropsychiatry* 5, 132–148.

Tune, L.E. (2000). *Seminars in Clinical Neuropsychiatry* 5, 149–153.

Van der Mast, R.C. & D. Fekkes (2000). *Seminars in Clinical Neuropsychiatry* 5, 125–131.

Weiss, A.P. & S. Heckers (1999). *Psychiatric Research: Neuroimaging* 92, 61–74.

Woody, G.E. (1970). *American Journal of Psychiatry* 127, 683–686.

Woodruff, P. et al., (1997). *American Journal of Psychiatry* 154, 1676–1682.

Wylie, A. et al. (1995). *British Medical Journal* 311, 125.

Plants of the gods

Ethnic routes to altered consciousness

Elaine K. Perry

1. Introduction

The neurobiology of consciousness is a new area of investigation although neurochemicals have been used for thousands of years to alter conscious awareness. 'Sacred' plants induce changes in consciousness in a ritualistic context. The known active chemicals are mainly alkaloids, generally non addictive but potentially toxic. They interact with specific transmitter systems—most commonly monoaminergic and cholinergic. 'Plants of the gods' have been used for as long as records are available. Evidence that for example *Datura* [thornapple], containing hallucinogenic muscarinic cholinergic receptor antagonists, was used ceremoniously in prehistoric times is indicated by the discovery of 'spiked' or 'hobnailed' ceramic forms, resembling the spiny fruits, in archaeological sites in Southwestern US and Mexico (Litzinger, 1981).

Alterations in consciousness induced by such plant chemicals include hallucinations or visions, experienced in euphoric trance-like states and often interpreted as spirit contact or possession, inspiration and enlightenment, self dissolution or cosmic union. As for traditional plant medicines, selection of 'plants of the gods' and appropriate dosage was empirical, based—long before any neuropharmacological knowledge—on a process of trial and error. It is remarkable that identification of the active constituents of these plants in the last century has demonstrated interactions with key transmitter systems implicated in the neurobiology of consciousness.

Plants containing indoleamines include: Psilocybe mushrooms, morning glory and Virola. Plants containing tropane alkaloids such as the muscarinic antagonists scopolamine and atropine are found in some members of the Solanaceae plant family—including datura, mandrake, henbane and

belladonna. Catecholamine-like alkaloids such as mescaline occur in Peyote and San Pedro catci. The opium poppy and cannabis contain chemicals such as opioids and cannabinoids which interact with other transmitter systems. Representive 'plants of the gods' from each group with particular neurochemical actions are illustrated in Figure 1.

This chapter emphasises, from an ethnopharmacological perspective, the importance of the role of particular transmitters in controlling conscious awareness; and also that achieving via pharmacological means a satisfactory or meaningful state of consciousness (however defined in personal or social terms) is a consistent human behaviour. Information on the relevant plant species, their ritualistic uses, active chemicals, and transmitter interactions is derived from two principal sources: ethnic accounts of subjective experience of altered consciousness induced by plant extracts; and objective chemical and pharmacological information on the active plant constituents and how these mimic or block the action of transmitters. There is a dichotomy in values : ethnic accounts focussing on perceived enhancement of mental experience, and much of the pharmacology on negative aspects such as induction of psychosis or toxicity.

2.   Enhancing consciousness?

> "We all possess pure, brilliant, expansive Fundamental Mind which remains unchanged throughout eternity. Its brilliance could not be matched by even a thousand suns rising together. This Mind is filled with complete wisdom possessed by each of us and is an inexhaustible treasure-house. And once the door to this treasure-house is opened, it reveals the greater wisdom and virtue and the ultimate in human dignity" (Venerable Songch'ol, 1994).

'Enlightenment' is traditionally achieved via meditation, music, chanting, dancing, sexual passion or ingestion of numerous chemicals mostly of plant origin. The German psychiatrist Kraeplin viewed pharmacopsychology—the use of pharmacological agents to explore the constitution of the psyche including consciousness—as an important scientific investigation. He did however consider this to be primarily a way of gaining insight into mechanisms of mental disease. A century later the subject of chemicals used to explore conscious experience continues to intrigue with recent texts such as "Food of the Gods" (McKenna, 1992); "The Alchemy of Culture" (Rudley, 1993); "Pikhal" (Ann & Alexander Schulgin, 1992); "Plants of the Gods" (Schultes & Hofmann, 1992); and "The Long Trip: A Prehistory of Psychedelia" (Devereux, 1997). Accord-

Amanita muscaria

Anadenanthera peregrina

Atropa belladonna

Banisteriopsis caapi

Cannabis sativa

Claviceps purpurea

Datura metel

Hyoscyamus niger

Figure 1. 'Plants of the gods'—representative species of the main categories referred to in this chapter.
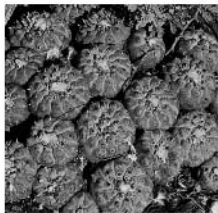
Lophophora williamsii

Mandragora officinarum

Papaver somniferum

Psilocybe caerulescens

Salvia divinorum

Tabernanthe iboga

Turbina corymbosa

Virola theiodora

Figure 1. (continued)

ing to Paul Devereux our culture is distinct in human history because of the difficulty in accepting the role of natural chemicals in 'aiding mind expansion'. However the guided, dose-controlled use of such chemicals in traditional ritualistic settings is not directly comparable to recent recreational or inadvertent use of plant preparations, particularly those selected for high potency.

'Sacred' plants can be considered in neurochemical categories, according to how the active chemicals interact with specific transmitter systems. In some instances more than one system is implicated, and in others the plants are used in complex mixtures. Much of the following discussion on the different species, their uses and active chemicals, is derived from the highly informative books by Schultes and Hofmann (1992) and Devereux (1997), and ethnopharmacological information not referenced is from these sources.

3. Indoleamines

Plant derived indoleamines, resembling 5-HT, include 5-methoxydimethyl tryptamine [bufotenine], psilocin, psilocybine, lysergic acid amides and dimethyltryptamine (DMT), one of the most powerful hallucinogens. DMT and bufotenine occur for in example seeds from the *Anadenanthera* tree, used as a snuff called Yopo by South American Indians.

Following the accidental discovery of the hallucinogenic properties of LSD, a synthetic derivative from ergot (*claviceps purpura* the fungal infection of rye containing alpha-lysergic acid dielthylamide), the Swiss chemist Albert Hoffman later identified similar structures of the ergot alkaloids, d-lysergic amine and d-isolysergic acid amide, in morning glory seeds used ritualistically for centuries by Mexican Indians. At this point, half a century ago, neuropharmacology and ritualistic explorations of consciousness converged, to the incredulity of many. It has been argued that ergot, associated with outbreaks of psychosis and convulsions in those consuming contaminated flour—known as St Anthony's fire, played a role as ergotized beer in the Eleusian mysteries of ancient Greece celebrated annually near Athens (McKenna, 1992).

'Magic' mushrooms belong to the genus Psilocybe, and include *Psilocybe mexicana* and *hougshagenii*, traditionally considered to be most important, and also *Stropharia cubensis* and *Panaeolus sphinctrinus*. These contain psilocybine and psilocine which mimic the action of serotonin. The Mazatec shaman, Maria Sabina, described the effects of the mushrooms as follows: "This is a world beyond ours, a world that is far away, nearby and invisible. And this is where God lives, where the dead live, the spirits and the saints, a world where

everything has already happened and everything is known. That world talks. It has a language of its own. I report what it says. The sacred mushroom takes me by the hand and brings me to the world where everything is known."

The Convolvulaceae family of vines include *Turbina corymbosa*, also known as ololiuqui or morning glory. Related species used in Mexico include *Ipomoea violaceae*, the seeds of which are hallucinogenic. Valued as sacred hallucinogens, the use of these vines dates back to ancient Aztec ceremonies. Morning glory is still used today by shamans in divination or healing procedures. The seeds of such vines contain lysergic acid alkaloids such as lysergic acid amide.

Virola species are used as hallucinogenic snuffs which are believed to promote contact with the spirit world. These species, which number over 50, include *Virola calophylla*, *elongata* and, most frequently used, *theiodora*. A red resin from the bark is smoked to generate prophesy, divination and diagnosis of disease. After a period of stimulation and hyperactivity there follows disturbed sleep with nightmarish hallucinations. The resins contain indole alkaloids such as N-methyl-tryptophan methyl ester. Other ingredients of Virola snuff mixtures include include Justica pectorans, from which no alkaloids have been isolated (Macrae & Towers, 1984).

3.1   Serotonergic mechanisms

Understanding the mechanism of action of naturally occurring hallucinogenic indoleamines has largely depended on research on the neurobiological effects of LSD. As discussed in Chapter 12, LSD induces changes conscious awareness beyond visual and other sensory hallucinations, apparently providing new insights on self-nature, loss of ego or self-identity and sensations of 'emptiness' or being 'undifferentiated'. Such mystical or spiritual experiences closely resemble those associated with sacred plants containing hallucinogenic indoleamines. LSD increases brain levels of 5-HT and, via autoreceptors, inhibits the firing of brainstem raphé neurons, diminishing the inhibitory action of the transmitter. The discovery of selective binding to the $5\text{-}HT_2$ receptor subtype (Glennon et al., 1984), focussed attention on this receptor as the primary target. Neurophysiologically LSD is a potent partial agonist at cortical 5-HT2 receptors (Marck & Aghajanian, 1996). There is a strong correlation between the dose of different chemicals required to induce hallucinations, and the concentration of the chemical which binds to human brain $5\text{-}HT_2$ receptors in vitro (Sadzot et al., 1989). These receptors are concentrated in the cerebral cortex, particularly in cingulate and other frontal regions, some areas in the temporal lobe (Fig. 2)
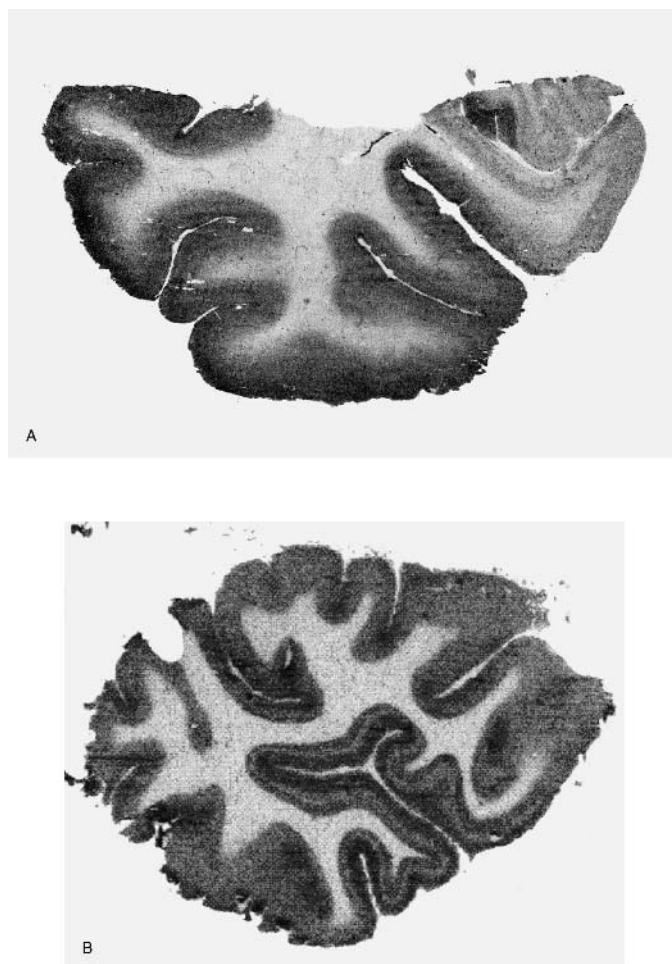
Figure 2. A. Distribution of the serotonin receptor, 5-HT2 subtype which binds the indoleamine hallucinogens, in human temporal cortex as indicated by the binding of radiolabelled ketanserin. While the receptor is relatively sparse in the hippocampal area and entorhinal cortex on the top right, it is concentrated in the temporal association cortex including the area concerned with visual association.

B. Distribution of the muscarinic receptor, M1 subtype which binds tropane hallucinogens such as scopolamine, in human occipital cortex as indicated here by the binding of radiolabelled pirenzepine. The receptor is concentrated in the visual striate cortex Brodmann area 17 (lower right area).

and in occipital cortex (visual layer IV), less dense in striatum and sparse in cerebellum (Pranzatelli et al., 1996; Busatto et al., 1997).

Consistent with the interaction of naturally occurring indoleamine hallucinogens with 5-HT2 receptors, Vollenweider et al. (1998) reported that psychomimetic effects of psilcybin were blocked dose—dependently by ketanserin (a 5-HT2 receptor antagonist), but not by dopamine antagonists such as haloperidol. There are also dopaminergic effects of ergot alkaloids. Using chemical imaging in vivo, Vollenweider et al. (1999) reported that psilocybin reduced raclopride binding (a measure of the occupancy of dopaminergic, mainly D2, receptors) in caudate and putamen, consistent with an increase in endogenous dopamine. The glutamate system has most recently been implicated in cognitive and perceptual effects, on the basis of 5-HT2 enhancement of the glutamatergic excitatory post synaptic potential in the cortex (Aghajanian & Marck, 1999).

4.   Phenylamines

Only a few of many naturally occurring chemicals based on the structure of endogenous catecholamines induce alterations in consciousness such as hallucinations. The most commonly used is mescaline, derived from the peyote cactus, *Lophophora wiiliamsi*. The dried mescal or peyote 'buttons' contain up to 30 alkaloids, mostly phenylethylamines, including trimethoxyphenylethyamine or mescaline. Peyote has been employed for thousands of years to induce 'fantastic' images associated with intense arousal, pleasure and well being. The hallucinogenic effects include kaleidoscopic, richly colored visions although other senses may also be involved. Changes in perception are primarily sensory, particularly visual, although in contrast to the indoleamines the boundaries between awareness of 'self' and 'non-self' are generally retained. Ordinary objects appear illuminated and marvellous—bathed in brilliant colours for example, and there is the conviction that this is a view of the essential nature of the universe. Experiences are associated with good humour and do not invoke fatigue, although tolerance develops if used regularly.

The psychologist, Havelock Ellis's account of a mescaline experience, cited by Hoffer and Osmond (1967) was as follows: "The visions never resemble familiar objects; they were extremely definite, but yet always novel; they were constantly approaching, and yet constantly eluding, the semblance of known things. I would see thick glorious fields of jewels, solitary or clustered, sometimes brilliant and sparkling, sometimes with a full rich glow. Then they would

spring up into flowerlike shapes beneath my gaze and then seem to turn into gorgeous butterfly forms."

There are also other non-monoaminergic alkaloids in some 'sacred' plants which enhance catecholaminergic function. The white and blue water lilies, *Nymphaea ampla* and *caerulea* were employed as hallucinogens in both the Old and New worlds. These species contain apomorphine (an opiate with dopamine agonist activity), together with nuciferine and nornuciferine.

4.1　Catecholaminergic mechanisms

Noradrenergic actions of mescaline are likely to account for increased arousal, and dopaminergic for reinforcing or pleasurable effects. The most relevant receptors involved in the effects of mescaline are not yet known. In a study of the distribution of radiolabelled mescaline in rodent brain (Korr, 1956), strong labelling of the hippocampus and amygdala was apparent. Interactions with the amygdala may account for the emotional content of the hallucinogenic experiences. On the basis of antipsychotic drug effects (Chapter 10), D2 and D3 may be the most important dopaminergic receptors involved. These are dense in striatal regions where they control circuitry converging from the entire cortex, via the basal ganglia to the frontal cortex. D3 receptors are not present in the cortex, but concentrated in the nucleus accumbens, the striatal region connecting with limbic cortex and amygdala, and also in thalamic nuclei such as the visual relay lateral geniculate nucleus. D2 receptors are also found in the thalamus and, in contrast to D3 also in the cortex, particularly temporal. Less is known of the distribution of α and β-adrenoreceptors in human brain although noradrenergic transporters are concentrated in thalamic nuclei such as the anteroventral (Chapter 1). In rodent brain highest densities of α-2 receptors occur in spinal cord, the raphe, locus coeruleus and vagus nuclei, with high levels in amygdala, hypothalamic nuclei and cortical areas such as entorhinal and insular (Unerstall et al., 1984).

5.　Ayahuasa—polypharmacology of the 'soul vine'

Ayahuasa is an Amazonian plant mixture with unique subjective effects (Freedland & Mansbach, 1999). Infusions are primarily based on the vine, *Banisteriopsis*, which is said to induce the sensation of the soul separating from the body. Ayahuasa is used in initiation ceremonies, for prophetic and divinatory purposes, or 'travelling in spirit', usually in the form of a bird or animal. Most infu-

sions contain additives, so that their full range and chemistry is not yet known. The active alkaloids of *Banisteropsis* are harmine, tetrahydroharmine and to a lesser extent harmaline. These β-carbolines inhibit the enzyme monoamine oxidase (McKenna et al., 1984), so preventing the breakdown of catechol and indoleamine transmitters.

Visions caused by such β-carbolines alone tend to be dull (blue or grey), but with additives, containing indoleamine alkaloids like DMT, the hallucinogenic effect is more potent and images more vividly coloured. Additives include *Psychotria viridis* and *carthenogensis* containing DMT. It is a Shamanic belief that these plants 'teach medicine' and they are referred to as 'doctor' or 'plant teachers' (Luna, 1984). As noted by Devereux, the range and chemistry of ayahuasa drinks, which number over 20, each used by the Harakubet Indians for specific visionary effects and symbolism, "reveal the sophisticated neurophysiological knowledge possessed by numerous generations of rain forest Indians." By comparison, information on mechanisms whereby individual hallucinogenic chemicals alter consciousness is limited. There are also constituents in ayahuasa yet to be identified such as those in the Psychotria species, e.g. carthagenensis, which is devoid of alkaloids (Leal & Elizabetsky, 1996).

In 1993 a multinational biomedical investigation of the effects of ayahuasa was conducted in an attempt to apply contemporary research models to the ceremonial use of plant hallucinogens (Grob et al., 1996). Conclusions were that the extract was associated with remission of psychopathology, and high 'functional status' with no detrimental effects on personality or cognition. In a report on elevated 5-HT uptake sites in platelets of ayahuasa users, Callaway et al. (1994) from Kuopio University Department of Pharmacology and Toxicology suggested that, if indicative of decreased 5-HT, this should not be interpreted as being associated with the development of neurological or psychiatric illness.

Other beta-carboline containing species are recorded for their ceremonial uses. *Peganum harmala* or Syrian rue also contains harmine, harmaline and tetraharmine, with semi-sacred uses as an hallucinogen in religion and 'magic'. This plant may, according to Schultes and Hoffman, have been the source of Soma or Huoma in ancient Persia and India. There has been extensive speculation, with no agreement so far, about the nature of soma, including Amanita, morning glory, ergot and psilosybine mushrooms (McKenna, 1992; Reidlinger, 1993).

Like Ayahuasa, Yopo from the beans of the *Anandenthera colubrine* tree which are smoked or taken as snuff by Argentinian Indians to induce halluci-

nations and communication with the spirit world, contains both beta carbolines and tryptamine derivatives.

6. Anticholinergics

Plants containing tropane alkaloids are used as prevalently in ritualistic contexts as those with monaminergic activities. Amongst 'plants of the gods' listed by Schultes and Hofmann, tropanes are present in 40% of species with known active ingredients. These consist of a variety of alkaloids which include principally hyoscine (scopolamine), d-hyoscyamine (atropine) and l-hyoscyamine, and also apoatropine, cuscohygrine, calystegine and tigliodine (Griffin et al., 2000). Such chemicals are potent muscarinic cholinergic receptor antagonists that induce hallucinations, unlike those described above, mainly characterized by visions of generally familiar animals and people. This feature is of particular interest in the context of Shamanic rituals. In aboriginal cultures of both North and South America such plants were, and still are, employed in initiation-rites. For example, the Indians of South Western California 'prescribed' extracts of Datura (species such as *Datura stramonium*, *inoxia* and *spinosa*) to adolescents at puberty. The particular animal which appeared in the resulting visions was considered to be the 'guiding spirit' of that individual.

Henbane (*Hyoscamus niger*) is thought to be the plant used as inhaled smoke in ancient Greece by priestesses to the Oracle of Delphi, to induce 'dementia' and evoke prophecies. The German toxicologist Gustav Schenk reported in 1955 after experimenting with the fumes from henbane seeds: "There were animals which looked at me keenly with contorted grimaces and staring terrified eyes . . . at the same time I experienced an intoxicating sensation of flying . . . I soared where my hallucinations—the clouds, herds of beasts—were swirling along."

In medieval Western Europe, deadly nightshade (*Atropa belladonna*) and mandrake (*mandragorum officinale*) (so respected that the root was removed from the earth by a dog rather than by human hand) were ingredients of witches 'brews'. Belladonna was used in 'flying ointments' by medieval witches, who practised the ancient tradition of 'flying women', embarking in a trance-like state on a 'spirit flight'. In some ethnic texts, such anticholinergic plants receive a low profile which may reflect negative perceptions of hexing, criminal uses and toxicity. In the middle ages for example mandrake was also used in the seduction of women, while victims of robbery in contemporary South American cities such as Bogota have been exposed to henbane extracts to induce obe-

dience and amnesia. Atropine, the principal alkaloid in such Solanaceae species was named after Atropos, the third and most deadly of three Greek fates who finally cut the thread of life. Angel's trumpet (Datura) has led to accidental death in youths using leaves and flowers as a substitute for LSD (Neiss et al., 1999).

Descriptions of subjective effects of tropane alkaloids in medical or scientific reports relate to recreational use or iatrogenic drug effects. In Texan adolescents, hospitalised after ingesting Jimson "Loco" weed (*Datura stramonium*), visual hallucinations included "insects on the walls" or "being chased by sharks" (Shervette et al., 1979). Visions of atropine-treated patients in Massachusetts, reported by Fisher (1991), included: "his mother who had been dead 25 years," "small boys downstairs in a detective's office," "11 men from a federal government agency" and "hundreds of marching British soldiers in yeomanry uniforms."

6.1 Cholinergic mechanisms

Cortical acetylcholine may play a particular role in conscious awareness, related to the process of selective attention (Chapters 2 and 3). It is thought to inhibit non relevant information, enhancing signal to noise ratios and 'confining the contents of the conscious stream' (Perry & Perry, 1995). Rather than acting as a direct excitatory signal, acetylcholine modifies the response of neurons to other transmitters such as GABA or glutamate (Chapter 1). Muscarinic receptor blockade by chemicals like atropine and scopolamine is likely to be particularly important in areas like the cerebral cortex where receptors are concentrated, presumably countering suppression of extraneous information and increasing awareness of pre- or unconscious information processing.

There are 5 muscarinic receptor sub-types of which M_1 is concentrated in cortex and striatum, M_2 in cerebellum, M_3 in thalamus and M_4 in striatum. M_1 is also high in occipital (visual) cortex (Fig. 2) and the lateral geniculate nucleus visual relay nucleus in the thalamus (Ferrari-Dileo et al., 1994). In vivo imaging using PET and a relatively non specific muscarinic antagonist (QNB derivative) has demonstrated highest binding in striatum and cortex, intermediate in thalamus and pons, and lowest in cerebellum (Zubieta et al., 1998). Using benztropine, more closely related to atropine, Ono et al. (1996) found highest densities in striatum and specifically occipital cortex. The tropane alkaloids are partially selective binding with greater affinity for the M_1, M_3 and M_4 than M_2 types, so hallucinogenic effects probably involve cortex (particularly visual), thalamus and perhaps also striatum.

Why antimuscarinics induce images of familiar animals or faces, as opposed to the novelty of images associated with monaoaminergic plant chemicals, remains to be determined. The visions resemble hypnogogic hallucinations which can occur normally on falling asleep, rather than those during dreaming sleep. The transition from awake to non-dreaming sleep is accompanied by reduction in the firing of both basal forebrain and brainstem cholinergic nuclei, consistent with antimuscarinic effects. The sensation of flying, particularly common with for example belladonna, could relate to the blockade of muscarinic receptors in the basal ganglia, spinal tract relay neurons or thalamic nuclei associated with motor function.

Some 'sacred' plants contain alkaloids that may act on nicotinic as opposed to muscarinic receptors. *Rhynchosia phaseoloides* is a vine, thought on the basis of original paintings, to have been employed in ancient Mexico as a hallucinogen, which contains an alkaloid with curare-like activity. Similarly the red beans *Erythrina Americana*, believed to have been employed as a hallucinogen, contain alkaloids of the erythran type producing curare like effects. Genista or *Cytisus canariensis* used as a hallucinogen in Mexico, and *Sophora secundiflora* once similarly used in North America, both contain the nicotinic agonist cytisine which although not known to be specifically hallucinogenic may induce a kind of delirium. Broom or *Sarothamnus scoparius* is said to be hallucinogenic and contains sparteine which has nicotinic channel activity. The possibility that Iboga alkaloids are also nicotinic is discussed below. Tobacco itself, including species more potent than Nicotiana tabaccum, has been used in high doses by South American Shamans to induce 'out of body experiences', and 'night vision'. These effects might relate to inhibitory effects of nicotine and 5-HT raphé neurons.

7. Amanita muscaria — paradoxical pharmacology

The red-spotted mushroom *Amanita muscaria* or fly agaric, so called because of its insecticide action, contains the muscarinic agonist, muscarine together with muscimol (a GABA receptor agonist, which is hallucinogenic) and ibotenic acid [a non selective NMDA receptor agonist]. The first effects of the mushroom, which is used in many parts of the world, are reported to be invigorating with individuals breaking out into song, dance and laughter. The hallucinations which follow vary from ecstatic to demonic. Shamans using the mushroom have been noted to alternate between attacks of great animation

and moments of deep depression. Amanita muscaria can induce macropsia when sense of scale is lost and small objects appear greatly enlarged.

Whether muscarine is hallucinogenic is unclear. If so, this might relate to its action in first stimulating and then blocking, via autoreceptors, the cholinergic synapse. It is considered more likely that muscimol is the important chemical involved in inducing hallucinations since its content increases on drying the mushroom—the standard method of preparation for Shamanic use in Scandanavian countries. The chemical also survives unaltered on excretion which may account for the habit of consuming the urine of mushroom users. Muscimol inhibits GABA uptake into neurons and glia and is the prototype of synthetic uptake inhibitors, including tiagabine used in the treatment of epilepsy. In relation to hallucinogenesis it is not immediately apparent how enhancing GABA function [blocking uptake from the synapse], or stimulating NMDA and cholinergic receptors is relevant, since chemicals with the exact opposite actions are hallucinogenic (Chapter 11). Some kind of synergy or perhaps other active chemical constituent may exist.

8.   The opium poppy

The opium poppy (*Papaver Somniferum*) contains up to 40 alkaloids such as morphine, codeine, papaverine and laudanine. The principal application of such chemicals, extracted from the congealed latex in unripe seed capsules, is analgesia and sleep induction. More subtle alterations in consciousness are indicated by reports that pain is still present but less distressing. Opium also induces waking, dream-like states. Thomas De Quincey in his "Confessions of an English Opium Eater" described an exhilaration of spirit and endlessly unravelling 'streamers' of thought and rhapsodic speculation. He referred to "the reawakening of a state of eye often times incident to childhood … vast processions moved along … a theatre seemed suddenly opened and lighted up within my brain, which presented nightly spectacles of more than earthly splendour." De Quincey believed opium induced dreams to be artistically creative and used such dreams to this effect.

The plant alkaloids mimic the endogenous peptides enkephalins and endorphins (Chapter 12), which meditate nociception and sleep. There are three types of widely distributed oplate receptors. Mu receptors are concentrated in neocortex, striatum, thalamus, hippocampus, amygdala and spinal cord, delta receptors in neocortex and amydala, and kappa receptors in striatum, amygdala and hypothalamus (Mansour et al., 1988).

9. Iboga

The rainforest shrub *Tabernathe iboga*, native to equatorial Africa, is known as a hallucinogen in magico-religious contexts. It is used in Gabon and the Congo to seek information from ancestors and the spirit world. Iboga is also a powerful stimulant, facilitating extreme physical exertion without fatigue, and is non-toxic except in high doses. It is reported to induce feelings of detachment, rainbow effects round objects, and time lengthening. Subjective reports include: "I could see many colors in the air ... suddenly my father descended from above in the shape of a bird ... and enabled me to fly after him" (Schultes & Hoffmann, 1992).

The plant contains more than 10 alkaloids the most active of which is ibogaine. This chemical and its synthetic analogue, 18-methoxycoronaridine [18-MC], reduce addiction to morphine and cocaine in animal models, and are currently being explored for clinical use in these and other forms of addiction (Glick et al., 2000). Anti-addictive effects have been linked to countering hyperactivity in the mesolimbic dopaminergic system (Szumlinski et al., 2000). The alkaloids also reduce self administration of nicotine, and nicotine evoked release of dopamine in rats, indicating that they may act via nicotinic receptors (Glick et al., 2000; Maisonneuve et al., 1997). Inhibition of serotonin uptake evident for ibogaine but not 18-MC, is not thought to be an important mechanism (Wei et al., 1990). Ibogaine is however an inhibitor of binding to the NMDA receptor (Layer et al., 1996), with an affinity in the micromolar range.

10. Cannabis

Long before the present era of recreational use, *Cannabis sativa* had religious significance. Uses in this context in Egyptian, Greek and Chinese cultures date back over three thousand years. The psychoactive cannabinoids (see also Chapter 12) are most concentrated in the resin (hashish). Effects range from mild euphoria and a dream-like state in which time perception is altered, to exaltation and hallucinations. The Indian Vedas considered cannabis as one of the 'divine nectars', providing health, longevity and 'visions of the gods'. According to the founder of the nineteenth century French 'Club des Haschischins', Theophile Gautier: "Never had such waves of bliss filled my being, I was so much part of the wave that I understood for the first time what the existence of elementary spirits, of angels and souls separated from the body might be like."

Cannabinoids, are non-alkaloid phenols or phenolic terpenoids. The most active is tetrahydrocannabinol, interacting with receptors concentrated in the basal ganglia, hippocampus and cerebellum (Howlett et al., 1990). Highest cannabinoid receptor densities are apparent in the globus pallidus, substantia nigra (pars reticulata), dentate gyrus (hippocampus) and molecular layer of the cerebellum. Cannabinoids mimic the action of endogenous chemicals which include anandamide (the Sanskrit word for bliss being ananda), a derivative of arachidonic acid. Interestingly cannabis, like antimuscarinic agents, induces loss of memory, and anandamides inhibit muscarinic receptor binding (Lagalwar et al., 1999), suggesting a possible link between the mechanisms of action of cannabinoid and anti-muscarinic agents.

11.   Salvia divinorum

Mazatec Mexicans cultivate this species of sage which they also call ska Maria Pastora (leaves of the Virgin Mary) because they believe it is an incarnation of the Virgin Mary. The leaves are used in divinatory rituals. Shaman apprenticeship in Oaxaca starts with ingestion of this plant to become acquainted with 'the ways of heaven' before going on to use the stronger-acting morning glory and magic mushrooms (Valdes et al., 1983). *Salvia divinorum*, smoked or chewed as a quid, is reported to be a mild hallucinogen, generating images of "dancing colours in elaborate 3-dimensional design" often in landscapes of flowers and fruits: "I saw eidactic images that evolved to plants and flowers. These later became great fruits and seeds" (Valdes et al., 1983; Valdes, 1994). Salvia divinorum is currently grown in California and employed as a legal hallucinogen.

The active constituent, unlike most sacred plants with known active ingredients, (excepting cannabis) is non-alkaloid. The leaves contain the diterpene salvinorin A (also known as divinorum A). This is effective in doses from 200–300 micrograms which makes it one of the most potent naturally occurring hallucinogen-remarkable for a non alkaloid. The mode of action is not yet established. No interactions, in terms of displacement of binding at concentrations up to 10^{-5}M, have been found with any of the muscarinic, 5-HT, dopaminergic, noradrenergic, glutamate, GABA or neuropeptide receptors so far tested, or with monoamine oxidase (Siebert et al., 1994). This raises the possibility that there may be a new class of receptor and even perhaps endogenous ligand yet to be identified, analagous with the discovery of opiate and cannabinoid receptors and their endogenous ligands.

12. 'Sacred plant' potential for drug discovery

In almost half of the plants of the gods (41 of 96 species, described by Schultes and Hoffman, 1992) no active chemical constituent has yet been identified. These plants provide the prospect for new drug discovery. There are for example alkaloids yet to be identified. *Caesalpina sepearia*, a shrubby vine reputedly used as an hallucinogen in China for inducing communication with the spirits, contains an alkaloid of unknown structure. *Scirpus atrovirens* is one of the most powerful herbs of the Tarahumara of Mexico, who use it to protect against mental illness enabling users to see brilliantly colored visions and talk to ancestors, from which alkaloids have also been extracted but none identified as hallucinogenic. Other plants for which no alkaloid or other hallucinogenic component has yet been identified include: *Calea zacatechichi* used by the Chontil Indians of Oaxaca, referred to 'leaf of god', and claimed to induce visions seen in dreams that 'clarify the senses'; *Conocybe siligineoides*, one of the sacred intoxicating mushrooms of Mexico; *Cymbopogon densiflorus*, which is smoked in Tanganyika to induce dreams which are believed to fortell the future; and *Maquira sclerophiylla* used in Brazil as a potent hallucinogenic snuff.

Like *Salvia divinorum*, several hallucinogenic plants contain terpenes—non nitrogen-containing low molecular weight carbon ring compounds which may be active ingredients. *Ephilantha micromeris*, a hallucinogenic plant used by Tarahumara Indians contains triterpenes. *Helichrysun foetidum* is a herb, smoked in Zululand to induce trances, that contains diterpenes not yet identified as hallucinogenic. *Lagochilus inebrians* is a type of mint, roasted to make an intoxicating tea used in Turkestan which contains a diterpene. Nutmeg (*Myristica fragrans*) can in high doses induce hallucinations and the principal component myristicine is a terpene, which may be aminated on ingestion to form an amphetamine-like derivative (Devereux, 1997). Undiscovered psychopharmacological mechanisms based on the chemistry of such terpenes may exist that could provide new avenues for drug and drug target discovery. The essential oil of common sage, Salvia officinalis, containing of a variety of monoterpenes, has been shown to inhibit acetylcholinesterase and so have potential application in the treatment of dementia (Perry, N. et al., 1996).

13. Emerging Profiles

In conclusion, the following generalisations can be made:

- While there is a broad spectrum of transmitter systems targeted by chemicals in 'plants of the gods', those with monoaminergic and cholinergic activities are the most prevalent. Amongst the species described by Schultes and Hoffman, 90% of those with known active constituents contain chemicals with either monoaminergic (particularly 5-HT) or cholinergic activities. Interestingly none appear to contain both types of chemicals.
- Complex conceptual changes such as dissolution of the boundary between 'self' and 'non-self' are generally associated with chemicals like psilocybin which stimulate 5-HT_2 receptors.
- Novel, pleasurable visual images are induced via catecholaminergic activation by for example mescaline and, although not yet established, dopaminergic D2 and D3 receptors may be particularly relevant.
- Familiar imagery, particularly of people and animals, and also the sensation of flying, are commonly associated with muscarinic cholinergic receptor blockade induced by chemicals found in Solanaceae species such as mandrake and datura.
- Of the different sensory modalities, olfaction does not appear to feature in reports of the effects of plant hallucinogens. Since olfaction is the one sense not relayed through the thalamus, this brain area is likely to be central to the changes in consciousness described. Many target receptors implicated, e.g. muscarinic, 5-HT_2, D_2, D_3 and opiate, are present in this thalamic nuclei the human brain.
- New insights into neural networks involved in such alterations in consciousness are likely to arise from in vivo imaging in the presence and absence of plant extracts correlated with subjective reports. As recently reported for psilocybin, chemical imaging provides key information on brain areas and transmitter receptors involved.

14. Visions of reality?

Since the same chemical in different contexts induces hallucinations of local cultural significance, there is unlikely to be a specific mechanism related to spiritual or religious experience. While most would assume visions induced by chemical hallucinogens result from released memories or associative processes,

the shaman or practitioner of other spiritually-based ritualistic practices believes otherwise. For such users of 'hallucinogenic' plants, the visions are based on reality of the spirit world, which is not normally accessible to everyday consciousness. In the context of evidence, obtained in the absence of preconceived bias or belief, by independent observers the following are provocative:

- 'Reality' of Ayahuasa induced visions (Brennan, 1993): Michael Harner reported that he communicated with giant reptilian dragon creatures with pterodactyl-like wings, from whose carnivorous jaws gushed a torrential flood of water. They explain that they are escaping an enemy that created terrestrial life forms and are true masters of the universe. Harner, troubled by these visions, eventually sought the advice from an old Conibo Indian shaman who assured him 'they' are always saying this but are only masters of outer darkness. Harner was stunned—he had apparently visited a world well known to the shaman from personal experience.
- Divination/precognition induced by Ayahuasa (Harner, 1973): Anthropologist, Kenneth Kensinger was informed at an ayahuasa party, by six out of nine Peruvian Cashinahua present, of the death of his father in law which he was later informed by radio had occurred two days before.
- Mazatec mushroom images materialise (Riedlinger, 1990): Allan Richardson in 1955 experienced visions including a portrait of a Spanish cabellero above a mantelpiece. On returning to Mexico city he entered a hacienda not previously visited and saw the portrait of his vision in the drawing room ... he was still puzzling over this 35 years later!

Whilst the use of exogenous chemicals may induce such 'transcendental' experiences, non pharmacological—for example cognitive—strategies although more challenging, may offer a safer and more satisfying option. A Japanese poet, and practitioner of Zen Buddhism reported the effects of MDMA as follows: "It has taken twenty years of studying Zen for me to reach this clarity, but I am glad I did it my way" (Saunders, 1993).

Acknowledgement

References

Aghajanian, G.K. & G.J. Marek (1999). *Neuropsychopharmacology* 21, 16S–23S.
Brennan, J.H. (1993). *Ancient Spirit.* London: Warner.
Busatto, G.F. et al. (1997). *European Journal of Nuclear Medicine* 24, 119–124.
Callaway, J.C. et al. (1994). *Psychopharmacology* 116, 385–387.
De Quincey, T. (1821). *Confessions of an Opium eater.* London: Dent, 1960.
Devereux, P. (1997). *A Prehistory of Psychedelia.* USA: Penguin.
Ferrari-Dileo, G.M. et al. (1994). *Molecular Pharmacology* 46, 1028–1035.
Fisher, C.M. (1991). *Canadian Journal of Neurological Science* 18, 18–27.
Glennon, R.A. et al. (1964). *Life Sciences* 35, 2505–2511.
Glick, S.D. et al. (2000). *Neuroreport* 11, 2013–2015.
Gouzoulis-Mayfrank, E. et al. (1999). *Neuropsychopharmacology* 20, 565–581.
Griffin, W.J. & G. Lin (2000). *Phytochemistry* 53, 623–637.
Harner, M.J. (1973). Hallucinogens and Shamanism. New York: Oxford University Press.
Hoffer, A. & H. Osmond (1967). The Hallucinogens. New York: Academic Press.
Holzman, R.S. (1998). *Anesthesiology* 89, 241–249.
Howlett, A.C. et al. (1990). *Trends in Neuroscience* 13, 420–423.
Korr, H. (1975). *Callithrix jacchus. Psychopharmacologia* 46, 115–117.
Lagalwar, S. et al. (1999). *Journal of Molecular Neuroscience* 13, 55–61.
Layer, R.T. et al. (1996). *European Journal of Pharmacology* 309, 159–165.
Leal, M.B. & E. Elisabetsky (1996). *Journal of Ethnopharmacology* 54, 37–40.
Leander J. et al. (1983). *Journal of Ethnopharmacology* 7, 287–312.
Luna, L.E. (1984). *Journal of Ethnopharmacology* 11, 123–133.
Litzinger, W.J. (1981). *Journal of Ethnopharmacology* 4, 57–74.
McKenna, T. (1992). *Food of the Gods.* London: Rider.
McKenna, D.J. et al. (1984). *Journal of Psychopharmacology* 10, 195–223.
Macrae, W. & G.H. Towers (1984). *Journal of Ethnopharmacology* 12, 93–111.
Maisonneuve, I.M. et al. (1997). *Psychopharmacology* 129, 249–256.
Mansour, A. et al. (1987). *Journal of Neurosciences* 7, 2445–2464.
Niess, C. et al. (1999). *Deutsche Medicinische Wochenschrift* 124, 1444–1447.
Ono, S. et al. (1996). *Kaku Igaku* 33, 721–727.
Perry, E. (1995). *International Journal of Geriatric Psychiatry* 10, 1093–1094.
Perry, E.K. & R.H. Perry (1995). *Brain Cognition* 28, 240–258.
Perry, E.K. et al. (1999). *Trends in Neurosciences,* 22, 273–280.
Perry, N. et al. (1996). *International Journal of Geriatric Psychiatry* 11, 1063–1069.
Pranzatelli, M.R. et al. (1996). *Journal of Clinical Neuropharmacology* 19, 507–514.
Riedlinger, T.J. (1993). *Journal of Psychoactive Drugs* 25, 149–156.
Riedlinger, T.J. (1990). *The Sacred Mushroom Seeker.* Portland: Dioscorides Press.
Rudgley, R. (1993). *The Alchemy of Culture.* London: British Museum Press.
Sadzot, B. et al. (1989). *Psychopharmacology* 98, 495–499.
Saunders, N. (1993). *E for Ecstasy.* London: Nicholas Saunders.
Shervette, R.E. et al. (1979). *Pediatrics* 63, 520–523.
Shulgin, A. & A. Shulgin (1991). *Pihkal.* Berkeley, California, Transform Press.

Schultes, R. & A. Hofmann (1992). *Plants of the Gods.* Rochester, Vermont, Healing Arts Press.

Siebert, D.J. (1994). *Journal of Ethnopharmacol* 43, 53–56.

Songch'ol, Venerable (1994). *The Middle Way* 69, 42–43.

Szumlinski, K.K. et al. (2000). *Brain Research* 864, 13–23.

Unnerstall, J.R. et al. (1984). *Brain Research* 319, 69–101.

Vollenweider, F.X. et al. (1998). *Neuroreport* 9, 3897–3902.

Vollenweider, F.X. et al. (1999). *Neuropsychopharmacology* 20, 424–433.

Wei, D. et al. (1998). *Brain Research* 800, 260–268.

Zubieta, J.K. et al. (1998). *Journal of Cerebral Blood Flow and Metabolism* 18, 619–631.

Brain Pathology and Consciousness

Alzheimer's disease

Focus on the cholinergic system

Daniel I. Kaufer

1.   Overview

Freud (1891) coined the term *agnosia* to characterize a selective loss in the ability to recognize the meaning of nonverbal auditory stimuli, contrasting with primary disturbances in language function. Less than a decade later he postulated the *unconscious* mind as the repository of latent desires that gained access to conscious awareness only in the guise of dreams. For better or worse, this paradigmatic shift paved the historical divide between neurology and psychiatry in erecting a virtual barrier between the brain and mind. Freud's divergent approaches to awareness resonate with prevailing views on consciousness. Current trends focus on the neurobiological underpinnings of conscious awareness, a multiplex of neural processes spanning arousal, attention, and awareness that may individually submit to objective investigation and elaboration. Yet, there is an enduring tradition that views the phenomenology of consciousness (i.e. self-awareness) to be more properly addressed in the realm of subjective experience. Although both perspectives are not mutually exclusive (Farber & Churchland, 1995), identifying threads of convergence has proven elusive.

Alzheimer's disease (AD), the prototypical degenerative dementia of adulthood, provides a neurobehavioral template for examining conscious awareness in a natural disease model. The ensuing discussion centers on component processes affiliated with disturbed conscious awareness and their putative neuropathological substrates in AD, emphasizing the pre-eminent role of basal forebrain cholinergic deficits in prefrontal limbic circuitry. A focused review of clinical responses to therapeutic cholinergic manipulation will aim towards synthesizing objective and subjective clinical data impinging on altered awareness in AD.

2.   Clinical features

2.1 Cognitive

The insidious onset and gradual progression of disturbances in memory and other cognitive domains characterize AD. Although individuals with AD exhibit degrees of heterogeneity in their presentation and course of decline, the overall pattern of cognitive impairment is generally consistent. The initial manifestation typically involves difficulty remembering recent events, reflecting the selective disruption of episodic memory (anterograde amnesia, Zec, 1993). Whereas AD subjects exhibit early and prominent difficulties learning (storing) new information, defective recall of previously learned material (retrograde amnesia) is typically less severe early in the disease course (Table 1). In contrast to marked dysfunction in explicit memory processes that are dependent on context and conscious effort, implicit memory functions (e.g. procedural-learning) that reflect the unconscious facilitation of performance by previous experience are relatively preserved (Zec, 1993). Disturbances in language, visuoperceptual and visuospatial processing, and skilled motor functioning (apraxia) are other common early manifestations of AD. Performance deficits on complex attentional tasks (e.g. divided attention, dual-task performance), reflecting dysfunction in the central executive component of working memory, are also present early in AD and track with its clinical course (Baddeley et al., 1991). Impaired planning, judgement, decision-making, and problem-solving skills are typically evident. However, these pragmatic "executive" functions are often not assessed in routine cognitive screening evaluations because they are difficult to characterize objectively.

Agnosia is a hallmark of AD according to DSM-IV (APA, 1994), although not by its strict definition as a sensory modality-specific defect in recognition. The primary agnosia-related manifestation in AD is anosognosia, used to connote either unawareness of specific deficits or of general disability (Zec, 1993). It is principally in the latter sense, referring to impaired insight, that agnosia is

Table 1. Core cognitive deficits in Alzheimer's disease.

Cognitive Function	Exemplary Clinical Manifestations
Episodic memory	Inability to recall recent events
Executive functions	Impaired insight, judgement, planning
Language	Word-finding and expressive difficulties
Visual–perceptual	Getting lost in familiar areas
Praxis	Inability to operate appliances

included in diagnostic criteria for AD. In the former case, anosagnosia is tantamount to neglect, or sensory inattention, as might be seen with a nondominant parietal lobe lesion preventing an individual from recognizing that a contralateral limb is their own (Heilman et al., 1997). Although neglect and agnosia of sensory stimuli both occur in AD to a limited degree, faulty insight into the presence or severity of cognitive dysfunction is a more pervasive, and may be among the more clinically significant cognitive manifestations of AD (Seltzer, et al., 1997, Harwood et al., 2000).

2.2 Neuropsychiatric

Neuropsychiatric symptoms accompanying AD are more variably manifest than cognitive symptoms (Mega et al., 1996), but may contribute disproportionately to morbidity in both patients and their caregivers (Kaufer et al., 1998). Cognitive and neuropsychiatric symptoms in AD also differ fundamentally in how they are assessed. Whereas cognitive deficits are objectively evaluated by standardized neuropsychological tests in a clinical setting, compromised short-term episodic memory and insight renders an individual with AD unreliable as an informant. Neuropsychiatric disturbances in AD are usually documented by proxy, typically a family member or other caregiver, reporting on the individual's emotional and behavioral status in everyday life. Although it is misleading to view either cognitive or neuropsychiatric accompaniments of AD in strictly objective or subjective terms, conventional differences in how these signs and symptoms are assessed have important implications. For example, subjective bias on the part of an examiner should play little, if any role, in a standardized cognitive assessment. However, the results of such objective testing may provide only limited insight into functional cognitive capacities in everyday settings (Perry & Hodges, 1999). On the other hand, surrogate reporting of an AD individual's affective state, behavior, and personality traits may be heavily influenced by the very same characteristics in the informant. Notwithstanding the inherent subjectivity of assessing neuropsychiatric symptoms, a potential advantage relative to the clinical evaluation of cognitive deficits is that noncognitive symptoms reported are more likely to have a greater measure of ecological validity or "real-world" importance. The subjective clinical significance of neuropsychiatric symptoms in AD is underscored by the finding that about two-thirds of all such symptoms reported by caregivers were rated to be moderately to severely distressing to them (Kaufer et al., 1998a).

Neuropsychiatric disturbances in AD fall into five main categories, including personality alterations, mood disturbances, psychosis, disturbances of psy-

chomotor regulation, and neurovegetative signs (Table 2). Among these, only the first category, representing one's general mode of engaging the physical and social environment, is imbued with diagnostic relevance in AD (APA, 1994). Specifically, the core neuropsychiatric manifestation of AD is apathy or indifference, with a prevalence of about 60–70% in AD clinical populations (Mega et al., 1996; Kaufer et al., 1998a). Apathetic behaviors may be among the earliest clinical manifestations of AD and are variably manifest as decreased interest in hobbies or social activities, lack of concern, loss of initiative, reduced spontaneity, or social withdrawal (Kaufer & Cummings, 1995). Family members of individuals with AD often misreport apathetic behaviors as depression, which has a much lower prevalence of about 20% in AD (Ballard et al., 1996), and is distinguished by sadness and vegetative disturbances. Delusions and hallucinations occur in about half of all individuals with AD, most commonly in the form of paranoid delusions. Hallucinations, although present in AD, usually accompany delusions and are more characteristic of Dementia with Lewy bodies (see Chapter 16). Individuals with AD may exhibit a variety of aberrant motor behaviors such as agitated pacing, wandering, rummaging about, and fidgetiness.

AD subjects have a higher prevalence of sleep disturbances than normal elderly, including sleep fragmentation, advancement of the sleep-wake cycle, and decreased amounts of slow wave and rapid-eye movement (REM) sleep (Prinz et al., 1982; Reynolds et al., 1988; Bliwise et al., 1989). Sleep-wake cycle disruption in AD has been associated with a greater burden of neuropsychiatric disturbances (Rebok et al., 1991; Ancoli-Israel et al., 1994), particularly apathy and delusions (Kaufer et al., 2001). Several studies have observed a relationship between the degree of intellectual impairment and REM sleep abnormalities (Prinz et al., 1982; Vitiello et al., 1984; Moe et al., 1995), underscoring the role of REM sleep in memory consolidation (Wilson & McNaughton, 1994).

Table 2. Core neuropsychiatric symptoms in Alzheimer's disease.

Neuropsychiatric Domain	Exemplary Clinical Manifestations
Personality (social engagement)	Apathy, indifference, disinhibition (rare)
Mood/Emotions	Depression, irritability, euphoria (rare)
Psychosis	Paranoid delusions, hallucinations
Psychomotor	Wandering, pacing, agitation
Neurovegetative	Sleep-wake disturbances, hyperphagia (rare)

3.   Characterization and clinical correlates of impaired awareness

Anosagnosia, as a characteristic feature of AD refers to impaired awareness of functional disabilities (e.g. sensory, motor, cognitive). A variety of assessment strategies for awareness of deficits in AD have been employed, the most common being to ascertain a subject's level of insight into their deficiencies based on semi-structured or less formal clinician interviews (Reed et al., 1993; Lopez et al., 1994; McDaniel et al., 1995; Ott et al., 1996). Other methods of assessment include indirectly comparing discrepancies between self-ratings of memory and other functional deficits to ratings of the same areas by informant-caregivers (Michon et al., 1994; Ott et al., 1996), and the use of clinician-rated scales (Migliorelli et al., 1994) or scale items (Harwood et al., 2000) designed to evaluate deficit awareness. The varied methodology and item content used for evaluating degrees of awareness or insight in AD are likely to account for some of the conflicting data reported. For example, although anosagnosia in AD appears to be generally related to overall dementia severity (Lopez et al., 1994; McDaniel et al., 1995; Starkstein et al., 1997; Harwood et al., 2000), this has not been an invariable finding (Reed et al., 1993; Michon et al., 1994). The relationship between impaired awareness of deficit and depressive symptoms in AD is less clear. Several studies have observed inverse correlation between these symptom manifestations (Migliorelli et al., 1994; Starkstein et al., 1997; Harwood et al., 2000), while other studies have not (Reed et al., 1993; Michon et al., 1994; Lopez et al., 1994). One recent study (Derouesne et al., 1999) observed that unawareness of deficits in mild cognitively impaired AD subjects was generally more strongly correlated with noncognitive symptoms than cognitive deficits, particularly with respect to apathy. Most subjects were studied with single-photon emission computed tomography (SPECT), which showed decreased awareness to be positively correlated with frontal lobe perfusion deficits. Another SPECT study (Reed et al., 1993) reported unawareness of deficits in AD subjects to be correlated with decreased regional perfusion in the right dorsolateral frontal lobe. Confabulatory or false-positive errors on a recognition memory test were also positively correlated with anosagnosia, suggesting an interaction between disturbances in awareness, explicit memory processing, and self-monitoring. The latter study, which did not observe a positive relationship between awareness deficits in AD subjects and general cognitive status, together with one that did (Lopez et al., 1994), concur in their findings that impaired awareness was most strongly associated with performance deficits on "frontal-executive" cognitive tests. Ott and colleagues (1996), who emphasize the contribution of defective self-monitoring to anosagnosia in AD,

reported similar findings. Despite the varied methodologies employed, these data suggest a neurobehavioral framework for disturbed conscious awareness in AD that reflects the impaired ability to monitor and dynamically integrate behavioral output and internal state markers in forming flexible and accessible representations of self. In conjunction with aberrant explicit memory processing, reduced awareness of deficits is associated with compromise in diverse prefrontal-limbic functions, including the regulation of mood and motivational states, sensory-motor integration, and executive control processes (e.g. working memory).

4.   Pathological features

4.1   Structural pathology

The two major histopathological markers of AD are neurofibrillary tangles, composed of abnormally phosphorylated tau protein, and extracellular neuritic plaques, consisting of insoluble beta-amyloid protein (Arnold et al., 1991). Both types of pathology are topographically selective, primarily affecting neocortical association areas, and, in the case of neurofibrillary tangles, limbic (archicortical) and paralimbic (allocortical) regions. A staging system for AD has been described based on the regional density of neurofibrillary tangles (Braak & Braak, 1991). Neurofibrillary tangles are thought to first appear in nerve cell bodies of pyramidal neurons (layers II and V) in the entorhinal cortex. Neurofibrillary tangle involvement then spreads in a generally symmetric manner to the nearby hippocampus, parahippocampal gyrus, and amygdala, and from there to pyramidal neurons (layers III and V) in neocortical association areas located in the temporal, parietal, and frontal lobes. Primary sensory and motor regions of the cortex are relatively spared. The entorhinal cortex has been observed to be the gateway for the transfer of neocortical information to the hippocampus, suggesting that the initial manifestation in AD of episodic memory loss reflects the isolation of the hippocampus from its afferent sensory inputs (Hyman et al., 1990). Involvement of temporal, parietal, and frontal neocortical association areas in AD correspond to language, visuoperceptual, and frontal-executive deficits, respectively, and reflects the selective disruption of cortical–cortical and cortical–limbic association pathways emanating from layer III pyramidal neurons. Neurofibrillary tangle and neuritic plaque accumulation is accompanied by neuronal loss and reduced synaptic

density, the latter being among the most robust structural correlate of cognitive deficit severity identified to date (DeKosky et al., 1990).

4.2 Neurochemical pathology

Cholinergic. Since the initial reports over two decades ago of severe and selective deficits in central cholinergic markers in AD, acetylcholine has commanded much attention regarding its functional role in the disease. There are two main cholinergic projection systems, one in the brainstem, including the pedunculopontine and laterodorsal tegmental nuclei, the other in the basal forebrain, comprising the nucleus basalis of Meynert (nbM), medial septal nucleus, and the vertical and horizontal limbs of the diagonal band of Broca (Mesulam, 1995) (see also Chapters 1 and 2). In AD, the basal forebrain cholinergic system is markedly compromised, whereas the brainstem cholinergic system, which participates in the ascending reticular activating system (arousal) and the regulation of rapid-eye movement (REM) sleep, is typically affected to a lesser degree, if at all (Zweig et al., 1987; Woolf et al., 1989) (Table 3).

Basal forebrain cholinergic nuclei project to all cerebral cortical areas and the amygdala (nbM), hippocampal formation, cingulate, and hypothalamus (medial septal nucleus and vertical limb of the diagonal band), and the olfac-

Table 3. Central cholinergic projections in Alzheimer's disease (AD).

Cholinergic Source	Target	Functional Affiliation	Involvement in AD
Brainstem nuclei: pedunculopontine and laterodorsal tegmental	thalamic nuclei (various)	arousal/attention; sensory, motor, limbic	+/–
	pons/medulla	REM sleep	+/–
Basal forebrain nuclei: nucleus basalis	cerebral cortex: (association)	Executive, language, perceptual,	+++
	(primary)	sensory, motor	++
	amygdala	emotional processing	++++
Medial septum/VLDB			
	hippocampus	learning and memory (explicit)	++++
	anterior cingulate	attention/motivation	+++
	hypothalamus	appetitive regulation	++

VLDB – vertical limb of the diagonal band of Broca.

tory tubercle (vertical and horizontal limb of the diagonal band). The density of cortical cholinergic innervation is normally greatest in limbic (hippocampus and amygdala) regions, next highest in paralimbic areas (cingulate and orbitofrontal cortex), intermediate in neocortical association regions, and least in primary sensory and motor areas (Geula,1998). These projections exert a modulatory influence on a variety of cerebral processes, including attention, learning and memory, motivational and emotional state, sensory processing, and motor output. A remarkable feature of prefrontal cortical cholinergic innervation is its plurality, including direct projections from the nucleus basalis, both direct and indirect thalamic relay projections deriving from pedunculopontine nuclei, and an indirect influence from modulatory effects of striatal cholinergic neurons on striato-thalamo-cortical circuit activity (Perry & Perry, 1999). The functional characteristics of multiple cholinergic inputs to prefrontal regions are unknown, but may entail both global and regionally-selective modulatory influences on prefrontal neural activity.

The principal locus of cholinergic system pathology in AD is presynaptic, involving the marked and progressive loss of choline acetyltransferase (ChAT) over the course of the disease. The presumed loss of ChAT early in the course of AD has recently been challenged (Davis et al., 1999), but remains controversial. The topography of ChAT deficiency in AD is regionally selective and generally parallels the distribution of neurofibrillary tangles. The loss of ChAT activity in AD also tends to be most severe in cortical areas where it is normally most abundant, namely, medial temporal limbic and temporal, parietal, and frontal neocortical association areas (Proctor et al., 1988). Reductions in acetylcholinesterase (AChE), the degradative enzyme for acetylcholine, are generally similar in topography and extent as those of ChAT. Decreased numbers of nicotinic cholinergic receptors have been reported in the cortex and medial temporal regions of AD patients (Newhouse et al., 1995). Central nicotinic receptor-mediated effects include the stimulated release of other neurotransmitters, particularly dopamine. Muscarinic cholinergic receptors are much more abundant in the central nervous system than nicotinic receptors, and are thought to play a greater role in cognitive deficits associated with AD (Cutler & Sramek., 1995). Among muscarinic receptor subtypes, presynaptic M2 receptors are diminished in AD, particularly in the hippocampus, whereas M1 receptors are spared until later in the disease course.

Monoaminergic.   AD also affects the ascending monoaminergic brainstem systems, including dopamine (ventral tegmental area), norepinephrine (locus coeruleus), and serotonin (raphe nuclei), which parallel the central choliner-

gic system in their wide distribution and multiple modulatory influences. The variable degree of involvement of central monoaminergic projection systems in AD is more akin to the brainstem than basal forebrain cholinergic system, yet may contribute to a variety of neuropsychiatric symptoms (Palmer & DeKosky, 1993). Norepinephrine plays a central role in the maintenance of arousal and processing salient external events, and is implicated in regulating mood and anxiety level (Robbins & Everitt, 1995). Neuronal loss in the locus coeruleus of AD patients has been reported to correlate with depressive symptoms in some (Zweig et al., 1988; Zubenko & Moossy, 1988), but not all (Hoogendijk et al., 1999) studies. Serotonergic deficiency is strongly implicated in mood and psychotic disturbances, and markers of serotonergic activity are typically reduced in AD (Zweig et al., 1988; Palmer et al., 1988; Chen et al., 1996). Decreased serotonergic markers in AD have been equivocally correlated to depression, psychosis, and aggression. Dopaminergic activity is even less affected in AD compared to the generally modest reductions in other monoaminergic transmitters relative to the basal forebrain cholinergic system (Hoogendijk et al., 1999). As aberrant dopaminergic transmission is strongly linked to deficits in working memory, psychosis, and abnormal motor activity in disorders such as schizophrenia and Parkinson's disease, where dopaminergic alterations are prominent, dopaminergic dysfunction *per se* presumably contributes modestly to altered consciousness in AD.

5.   Cholinergic–monoaminergic interactions

The paradigmatic example of cholinergic–monoaminergic interactions is sleep-wake cycle regulation, where acetylcholine and norepinephrine both promote arousal, but are reciprocally active or quiescent during periodic alternations between REM and non-REM sleep. Serotonin has an inhibitory effect similar to norepinephrine on brainstem cholinergic neurons that are active during REM sleep (Hobson & Steriade, 1986). In AD, disturbances in arousal and REM sleep activity are much less prominent than in degenerative brain disorders where Lewy body pathology in monoaminergic brainstem nuclei is a primary (Parkinsons's disease) or characteristic (Dementia with Lewy bodies) feature (Chapters 15 and 16). The severe involvement of basal forebrain cholinergic nuclei and attendant cholinergic deficiency in AD is conjoined with lesser and more variable degrees of monoaminergic deficits.

Cholinergic–monoaminergic interactions at multiple neuraxial levels comprise the principal neurochemical substrates of consciousness. In AD, altered

consciousness primarily reflects the loss of cholinergic modulatory influences in the setting of relatively preserved monoaminergic inputs. The paucity of dopaminergic deficits in AD, in particular, would be expected to yield marked imbalances in cholinergic–dopaminergic interactions, which may contribute to psychotic symptoms, motor hyperactivity, working memory deficits. Working memory, as the conscious, effortful, and volatile prefrontal focus of ongoing selective attention, provides the raw material for explicit learning and memory formation, and plays a crucial role in mediating awareness among transactions between internal cues and environmental information.

Alterations in cholinergic interactions with dopamine and other mono-amine transmitters in AD are superimposed on a selectively compromised substrate of cortico-cortical and cortico-limbic neural pathways. As clinical deficits reflect the combined effect of structural neuronal (and synaptic) loss and altered neuromodulatory input into surviving neurons, discerning the relative contribution of structural and neurochemical deficits is problematic. However, the recent introduction of cholinergic augmentation therapy for AD provides a pharmacological probe for isolating the contribution of cholinergic deficits to cognitive and neuropsychiatric symptoms, and allied disturbances in consciousness. In this context, clinical symptoms ameliorated by cholinergic therapy may either reflect direct actions of cholinergic repletion or indirect effects reflecting a normalized balance of cholinergic–monoaminergic modulatory tone.

6.   Cholinergic contributions to conscious awareness

A review and analysis of deficit correlational studies in AD highlights the role of prefrontal-limbic circuitry as the functional neuroanatomical focus of conscious awareness. A more comprehensive and detailed perspective on conscious awareness in AD, specifically in relation to cholinergic deficits, has been elaborated by Elaine Perry and colleagues (Perry & Perry, 1995; Perry & Perry, 1999; Perry et al., 1999). A central theme of this seminal body of work, postulating a widely distributed and diverse role of acetylcholine with respect to component processes affiliated with conscious awareness, stands in stark contrast to the timeworn, yet influential "cholinergic hypothesis" of memory in AD (reviewed in Francis et al., 1999). The historical legacy of the cholinergic hypothesis, perhaps reminiscent of Freud's theory of the unconscious, was to advance therapeutic efforts aimed at reversing the cholinergic deficiency in AD, with a primary focus on general cognitive outcomes, and a secondary focus

on measures of explicit learning and memory. A critical observation advanced contemporaneously with the cholinergic hypothesis was that cortical cholinergic modulatory influences act to optimize the detection of signal relative to background "noise," thereby enhancing the fidelity of information processing (Drachman & Sahakian, 1979). In extrapolating this principle of cholinergic function to a network systems level of analysis with respect to conscious processing, Perry and Perry (1995: 245) have suggested that "cortical acetylcholine is involved in selecting the most currently relevant information into the conscious stream from the massive parallel information processing that occurs at the subconscious level." In the following section, the relevance of this postulate to acute treatment responses in AD subjects to cholinergic-enhancing drugs is explored.

7.   Cholinergic treatment

7.1   Cognitive responses

Several cholinesterase-inhibitor (ChEI) drugs, including tacrine, donepezil, rivastigmine, and galantamine have been shown to have consistent, if generally modest and highly variable, benefits on general cognitive functioning in AD. Relatively few studies have examined the effect of such treatments on individual cognitive domains, particularly those involving complex attentional and executive functions. An early study of tacrine in AD assessed patients on a battery of computerized tasks involving attention, learning, and memory (Sahakian et al., 1993). These investigators reported a beneficial effect of tacrine on speed and accuracy in performing a 5-choice attentional task, whereas no effect was observed in performing a delayed matching-to-sample mnemonic task. Alhainen and colleagues (1993) observed improved performance in tasks of attention and orientation to be the most robust cognitive changes during acute tacrine treatment. Studies of nicotine in AD patients have generally shown improvement on attentionally-demanding task performance, with respect to decreased reaction times, improved sustained attention, and in one study, reduction in intrusion errors on a free-recall task (reviewed in Newhouse, 1997). The selective action of nicotine on attentional processes in AD has been suggested to reflect the drug effects on constraining the focus of attention by facilitating the inhibition of irrelevant stimuli. Although identifying elementary cognitive functions most responsive to cholinergic therapy in AD has received remarkably little attention, the data presented are consistent with the prominent role of cholin-

ergic systems in facilitating various attentional processes that may contribute to awareness.

7.2 Neuropsychiatric responses

There is burgeoning evidence supporting the therapeutic potential of ChEI drugs for a variety of neuropsychiatric manifestations in AD (Cummings & Kaufer, 1996, Cummings, 2000). Preliminary studies of tacrine in AD (Kaufer et al., 1996; Kaufer et al., 1998) observed significant reductions in apathy, disinhibited behaviors, anxiety, and aberrant motor behaviors (e.g. pacing, fidgeting) using a standardized neuropsychiatric symptom rating scale. Hallucinations were decreased by 50% in three of the six subjects with this symptom at baseline in one of these studies (Kaufer et al., 1996), but the small number of subjects precluded this finding from reaching statistical significance. A reduction in apathetic behaviors was the most robust symptom response overall, and was the only neurospsychiatric domain that was associated with cognitive improvement. A larger, retrospective study of tacrine reported improved cooperation and reduced pacing and delusions in active-treatment subjects relative to placebo (Raskind et al., 1997). A multicenter, placebo-controlled, double-blind study of the ChEI, metrifonate, showed significant differences favoring treatment relative to placebo in apathy, hallucinations, depression, and a trend favoring treatment for aberrant motor behaviors (Kaufer, 1998). A small open-label study of donepezil reported a virtually identical profile of symptomatic responses during a 12-week treatment period (Kaufer et al., 1998b). This study also included a 20-item measure of caregiver-rated treatment response domains assessing cognitive, behavioral, functional, and social-emotional aspects of everyday life. "General awareness" and "generally happier" were the two items showing the greatest net improvement during the treatment period, and the former correlated significantly with reduced apathy ratings. Overall, reductions in apathy and hallucinations appear to be the most consistent neuropsychiatric symptoms responsive to ChEI therapy, followed by aberrant motor behavior and depressed mood. Viewed together, treatment responses in these clinically defined neuropsychiatric domains suggest that a fundamental effect of cholinergic therapy in AD is to facilitate the processing and integration of personally (motivation and mood) and environmentally (sensory and motor) relevant stimuli. From a caregiver's perspective in the context of everyday life, cholinergic-mediated effects appear to enhance an AD subject's awareness of self and surroundings. A heuristic model summarizing the putative effects of
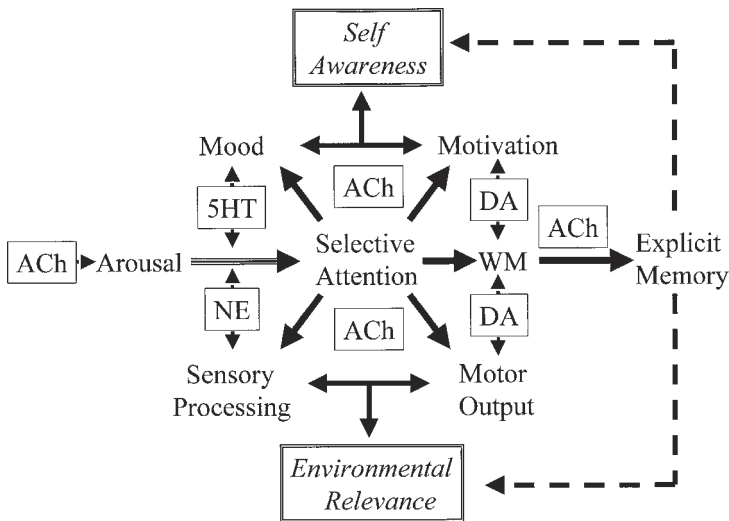
Figure 1. Therapeutic cholinergic modulation of conscious awareness in AD.

therapeutic cholinergic modulation on conscious awareness in AD with respect to monoaminergic transmitter interactions is presented in Figure 1.

8. Conclusions

AD offers fertile ground for investigating the phenomenology and neurobiology of disturbed awareness, representing a higher-order alteration in consciousness. Future investigations would benefit greatly from standardized assessments of awareness deficits in AD, including the use of complementary sources of objective and subjective data for corroborative and correlative purposes. Moreover, as anosagnosia refers specifically to impaired awareness of *disability*, extending the range of study to include general cognitive, affective, and social aspects of self-awareness (autognosis?) would provide a more comprehensive scheme for systematically referencing these different attributes of reflective conscious processing in relation to overt behavior. Finally, comparing areas of selectively retained awareness relative to those that were compromised within individuals with AD may enhance precision in identifying brain-behavior relationships in the arena of self-awareness.

A review of symptomatic therapeutic responses in AD to cholinergic-enhancing agents suggests that primary therapeutic effects include the focusing

of attentional and sensory processing, and the anchoring of mood, motivation, and motor behavior to environmentally and personally relevant stimuli. Although episodic memory deficits are the defining feature of AD, a broader view of the structural and cholinergic pathological features suggests that executive and specific attentional functions, and motivational aspects of behavior are integral components of conscious awareness, and are compromised early and severely over the disease course. This constellation of cholinergic-sensitive clinical symptoms is strongly affiliated to prefrontal-limbic circuitry, and has led to the hypothesis that this circuitry is the primary locus of clinically relevant cholinergic treatment effects (Kaufer et al., 1998; Cummings, 2000). Preliminary support for this hypothesis derives from a SPECT study demonstrating that cholinergic treatment responders tended to exhibit baseline perfusion deficits in inferior orbitofrontal and dorsolateral prefrontal regions (Mega et al., 2000). Recently developed functional neuroimaging methods using radioactive ligand-binding techniques have will allow for *in vivo* quantitative assessment of acetylcholinesterase activity before and during treatment with cholinergic agents (Kuhl et al, 1999). Beyond the immediate clinical implications, this method provides a powerful tool for generating and testing hypotheses regarding the functional anatomical and neurochemical components of conscious awareness in AD.

Axons from brainstem cholinergic nuclei (pedunculopontine and laterodorsal tegmental, double-line) form the ascending reticular activating system, which project to basal forebrain cholinergic and various thalamic nuclei in effecting cortical arousal. Ascending brainstem monoaminergic transmitters from the locus coeruleus (norepinephrine-NE) and raphe nuclei (serotonin-5HT) contribute to arousal, and participate in a variety of other cerebral functions (e.g. regulation of mood and sensory processing). These brainstem modulatory projection systems are typically affected to modest degrees in AD. Axons containing dopamine (DA) emanate from midbrain nuclei (substantia nigra and ventral tegmental area) and project to various forebrain structures, including the caudate and putamen (nigrostriatal pathway), limbic areas such as the nucleus accumbens and amygdala (mesolimbic pathway), and dorsolateral prefrontal cortex (mesocortical pathway). These dopaminergic pathways, which are typically little affected in AD, respectively influence motor activity, motivational and emotional state, and working memory processes. Therapeutic cholinergic manipulation in AD, presumably acting to reverse basal forebrain cholinergic deficits, has been demonstrated to improve aspects of selective attention, and ameliorate symptoms that reflect reduced motivation (apathy), mood disturbance (anhedonia), altered sensory processing (hallu-

cinations) and aberrant motor output (purposeless motor activity). Cholinergic augmentation in AD is also postulated to facilitate the integration of limbic-mediated information regarding prevailing internal states (mood and motivation) and externally-based sensory input and motor output. These integrative functions are likely mediated by working memory, which reflects moment-to-moment "on-line" conscious processing. Facilitated information processing in prefrontal association (working memory) and medial temporal hippocampal regions (explicit memory) is hypothesized to contribute to a temporally-integrated stream of conscious awareness that entails ongoing representational transactions between intrapersonal experience and extrapersonal events. The cholinergic-mediated restoration of spatiotemporal "binding" between internal state markers and sensory-motor functions in AD culminates in enhanced self-awareness and more environmentally-relevant perception and behavior.

References

Alhainen, K. et al. (1993). *Dementia* 4, 54–58.

American Psychiatric Association (1994). *Diagnostic and statistical manual of mental disorders, 4th ed.* Washington, DC: American Psychiatric Association Press.

Baddeley, A.D. et al. (1991). *Brain* 114, 2521–2542.

Ballard, C.G. et al. (1996). *International Journal of Geriatric Psychiatry* 11, 507–515.

Braak, H. & E. Braak (1991). *Acta Neuropathologica* 82, 239–259.

Chen, C.P.L-H. et al. (1996). *Journal of Neurochemistry* 66, 1592–1598.

Cummings, J.L. & D.I. Kaufer (1996). *Neurology* 47, 876–883.

Cummings, J.L. (2000). *American Journal of Psychiatry* 157, 4–15.

Cutler, N.R. & J.J. Sramek (1995). *CNS Drugs* 3, 467–481.

Davis, K.L. et al. (1999). *Journal of the American Medical Association* 281, 1401–1406.

DeKosky, S.T. & S.W. Scheff (1990). *Annals of Neurology* 27, 457–464.

Derouesne, C.S. et al. (1999). *International Journal of Geriatric Psychiatry* 14, 1019–1030.

Drachman, D.A. & B.J. Sahakian (1979). In: A. Barbear, J.H. Growdon, & R.Y. Wurtman (Eds.), *Nutrition and the Brain* (351–366). New York: Raven Press.

Farber, I.B. & P.S. Churchland (1995). In: M. Gazzaniga (Ed.), *The Cognitive Neurosciences* (1295–1306). Cambridge: MIT Press.

Francis, P.T. et al. (1999). *Journal of Neurology, Neurosurgery and Psychiatry* 66, 137–147.

Freud, S. (1891). Cited in Bauer, Russell M. (1993). In: K.M. Heilman & E. Valenstein (Eds.), *Clinical Neuropsychology*. *3rd edition* (215–278). New York: Oxford University Press.

Geula, C. (1998). *Neurology* 51(suppl 1), S18–S29.

Harwood, D.G. et al. (2000). *Neuropsychiatry, Neuropsychology, and Behavioral Neurology* 13, 83–88.

Heilman, K.M. et al. (1997). In: T.E. Feinberg & M.J. Farah (Eds.), *Behavioral Neurology and Neuropsychology* (309–318). New York: McGraw-Hill.

Hobson, J.A. & M. Steriade (1986). In V.B. Mountcastle (Ed.), *Handbook of Neurophysiology — The Nervous System, IV* (701–823). Bethesda: American Physiological Society.

Hooggendijk, W.J.G. et al. (1999). *Annals of Neurology* 45, 82–91.

Kaufer, D.I. & J.L. Cummings (1995). In: J. Ratey (Ed.), *Neuropsychiatry of Personality Disorders* (172–209). Cambridge, MA: Blackwell Scientific Publications.

Kaufer, D.I. et al. (1996). *Journal of Geriatric Psychiatry and Neurology* 9, 1–6.

Kaufer, D.I. et al. et al. (1998). *Journal of the American Geriatric Society* 46, 210–215.

Kaufer, D.I. (1998). *Dementia and Geriatric Cognitive Disorders* 9(suppl 2), 8–14.

Kaufer, D.I. et al. (1998). *Neurology, 50* A89.

Kaufer, D.I. et al. (2001). *Journal of Neuropsychiaty and Clinical Neuroscience* 13, 137.

Kuhl, D.E. et al. (1999). *Neurology* 52, 691–699.

Lopez, O.L. et al. (1994). *European Neurology* 34, 277–282.

McDaniel, K.D. (1995). *Alzheimer's Disease and Associated Disorders* 9, 101–104.

Mega, M.S. et al. (1996). *Neurology* 46, 130–135.

Mega, M.S. (2000). *Journal of Neuropsychiatry and Clinical Neuroscience* 12, 209–218.

Mesulam, M.-M. (1995). In: F.E. Bloom & D.J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* (135–146). New York: Raven Press.

Michon, A. et al. (1994). *Journal of Neurology, Neurosurgery and Psychiatry* 57, 805–809.

Migliorelli, R. et al. (1995). *Journal of Neuropsychiatry and Clinical Neuroscience* 7, 338–344.

Moe, K.E. (1995). *Sleep Research* 4, 15–20.

Newhouse, P.A. (1997). *Drugs and Aging* 11, 206–228.

Ott, B.R. et al. (1996). *Alzheimer's Disease and Related Disorders* 10, 68–76.

Palmer, A.M. et al. (1988). *Annals of Neurology* 23, 616–620.

Palmer, A.M. & S.T. DeKosky (1993). *Journal of Neural Transmission [Gen Sect]* 91, 135–159.

Perry, E.K. & R.H. Perry (1995). *Brain and Cognition* 28, 240–258.

Perry, E.K. & R.H. Perry (1999). In: B.L. Miller & J.L. Cummings (Eds.), *The Human Frontal Lobes: Functions and Disorders* (568–583). New York: Guilford Press.

Perry, E. et al. (1999). *Trends in Neurosciences* 22, 273–280.

Perry, R.J. & J.R. Hodges (1999). *Brain* 122, 383–404.

Prinz, P. et al. (1982). *Neurobiology of Aging* 3, 361–370.

Procter, A.W. et al. (1988). *Journal of Neurological Science* 84, 125–140.

Raskind, M.A. et al. (1997). *Archives of Neurology* 54, 836–840.

Reed, B.R. (1993). *Journal of Clinical and Experimental Neuropsychology* 15, 231–244.

Rebok, G.W. (1991). *Aging* 3, 193–196.

Reynolds, C.F. III et al. (1988). *Psychopharmacology Bulletin* 24, 43–48.

Robbins, T.W. & B.J. Everitt (1995). In: F.E. Bloom & D.J. Kupfer (Eds.), *Psychopharmacology: The fourth generation of progress* (363–372). New York: Raven Press.

Sahakian, B.J. et al. (1993), *Psychopharmacology* 110, 395–401.

Seltzer, B. et al. (1997). *Gerontologist* 37, 20–24.

Starkstein, S.E. et al. (1997). *British Journal of Psychiatry* 171, 47–52.

Wilson, M.A. & B.L. McNaughton (1994). *Science* 265, 676–678.

Woolf, N.J. et al. (1989). *Neuroscience Letters* 96, 277–282.

Zubenko, G.S. & J. Moossy (1988). *Archives of Neurology* 45, 1182–1186.

Zweig, R.M. et al. (1987). *Annals of Neurology* 22, 18–25.

Zweig, R.M. et al. (1988). *Annals of Neurology* 24, 233–242.

Zec, R.F. (1993). In: R.W. Parks, R.F. Zec & R.S. Wilson (Eds.), *Neuropsychology of Alzheimer's Disease and Other Dementias* (3–80). New York: Oxford University Press.

Parkinson's disease

Dag Aarsland and Randi Starrfelt

1.   Neurochemical changes in PD

Parkinsonism is a clinical syndrome characterised clinically by resting tremor, rigidity, bradykinesia, and postural changes. The most common causes are idiopathic Parkinson's disease (PD), secondary parkinsonism, and parkinsonism one to other neurodegenerative dementias such as dementia with Lewy-bodies (DLB). The prevalence of PD is about 100 per 100 000 population, with an age-dependent increase so that about 1% of elderly aged 65 or more are diagnosed as PD (Tandberg et al., 1995). Pathologically, PD is characterised by a marked loss of dopaminergic neurones in substantia nigra pars reticulata, with intra-neuronal Lewy bodies in the surviving cells. This results in a severe dopamine loss in the striatum. Dopamine losses of 80% or more are required for motor symptoms to develop. The most prominent dopamine loss has been found in the caudal portions of the putamen, with less than 1% of the dopamine remaining. Somewhat less pronounced loss was observed in the caudate head, although in the most dorsorostral parts, only 4% of the dopamine was remaining (Kish et al., 1988). PET studies suggest that dopaminergic caudate dysfunction in PD is associated with impairment of executive functions, working memory and attention, whereas the putaminal dopaminergic system is more closely related to motor symptoms (Rinne et al., 2000).

In addition to nigrostriatal dopamine deficits, several other cortical and subcortical regions are more or less affected. Monoaminergic brain stem nuclei such as the noradrenergic locus coeruleus (40–50% loss) and serotonergic raphe nuclei (20–40% loss) are commonly affected (Jellinger et al., 1999). The dopaminergic ventral tegmental area (VTA), medial to the substantia nigra and projecting to the hippocampus and prefrontal cortex including cingulate gyrus, is also commonly affected in PD.

Marked cholinergic disturbances are reported in PD. The two major cholinergic projecting pathways, the basal-forebrain neurons, projecting to the entire cortex, hippocampus and the thalamus, and the pedunculopontine-lateral dorsal tegmental neurons, projecting to the reticular formation and the thalamus, are both affected in PD with cell losses between 30% and 90% (Jellinger et al., 1999). Reductions in cholinergic activity, as measured by the level of choline acetyltransferase, have been reported to be even more extensive in neocortical regions, most extensive in frontal and parietal cortex, in PD (Perry et al., 1993). Nicotinic receptors are reduced, whereas muscarinic receptors (M1 Subtype) are (in compensation) increased in neocortical areas (Perry et al., 1993). This pattern of cholinergic changes in PD resembles that reported in DLB (Perry et al., 1993). Finally, the cortical changes in PD include frontal atrophy, cortical Lewy bodies, and Alzheimer-related pathology. In particular amyloid deposits are found in PD more often in those with dementia (Jellinger et al., 1999).

Accordingly, several of the neurochemical and neuroanatomical systems considered to be involved in arousal and consciousness, i.e. Meynert nucleus, pontine reticular formation, locus coeruleus and raphe nucleus with their cholinergic, noradrenergic and serotonergic afferents (Delacourt, 1995) are affected in PD. In addition, the dopamine system, in particular the mesolimbocortical system, is involved in cognition and motivation, and possibly in the emergence of positive psychotic symptoms such as hallucinations and delusions.

This chapter will review the behavioural changes in PD in terms of conscious and unconscious functions. It is based on the assumption of Delacourt (1995), that consciousness is not a separate faculty of mind, but rather depends on a certain activity mode of basic cognitive functions—attention, memory, perception, action planning and motivation. Changes in these domains of consciousness in PD patients are reviewed and in addition, since consciousness is closely associated with wakefulness, disturbances of sleep and dreaming in PD are also discussed.

2.   Behavioural changes in PD and role of the basal ganglia

Cognitive impairments are among the most common mental changes in PD, ranging from mild impairment of selected cognitive functions to severe dementia. In a study of more than 100 PD patients, only 25% performed adequately on a range of cognitive tests. Another 25% had mild impairment,

while the remaining 50% were demented (Janvin & Aarsland, 1999). The most commonly affected functions are attention, memory, executive and visuospatial functions (Taylor & Saint-Cyr, 1995). There is a six times increased risk for developing dementia in PD compared to normal elderly population (Aarsland, 2001a). Furthermore, minor or major depression is generally found in 40% of patients (Tandberg et al., 1996), hallucinations in 20–40%, (Aarsland, 1999a; Fenelon et al., 2000), and apathy (Aarsland, 1999b) and sleep disturbances (Tandberg et al., 1998; 1999) are also common. Recent studies have documented the clinical importance of neuropsychiatric symptoms with regard to caregivers quality of life (Aarsland, 1999c) and risk for nursing home placement (Aarsland, 2000).

There is relatively little known regarding the exact relationship between the neurochemical and structural brain changes and the behavioural changes in PD patients, although it is reasonable to assume that the extrastriatal pathologies contribute. The basal ganglia have usually been ascribed a role for motor functioning, but their role in behaviour regulation have been more recognised during the last decade. The basal ganglia are closely associated with the prefrontal cortex. The frontal cortex, in a topographical way, reaches virtually the entire striatum, and the output of the basal ganglia via the thalamus is primarily directed towards the frontal lobe (Groenewegen, 1999). Five segregated, parallel fronto-subcortical circuits have been identified, and three of these circuits are involved in the regulation of affective, cognitive and attentional functions (Alexander et al., 1986; Cummings, 1993). The activity within these circuits are modulated by direct and indirect nigrostriatal dopaminergic pathways. The direct pathway may function as an attentional amplifier, enhancing behaviourally relevant signals. The indirect path may operate to maintain focal attention by suppressing irrelevant signals (Jackson et al., 1994).

3. Disturbance of attention

Brown and Marsden (1998) hypothesised that the basal ganglia support a basic attentional mechanism operating to bind input to output in the executive forebrain. According to this hypothesis, the physiological basis for this attentional mechanism is to group together aspects of the distributed neuronal responses to sensory stimuli. Synchronisation of this kind may require normal basal ganglia function. Thus, in PD, in the cognitive domain, failure of synchronisation may lead to apathy and bradyphrenia.

According to Posner and co-workers (Jackson et al., 1994), the attention system can be divided into subsystems that perform different but integrated functions. Among these, there are three major functions that are of interest for the current discussion: a) orienting to sensory events; b) detecting signals for conscious processing, and c) maintaining a vigilant or alert state.

3.1 Orienting network

Anatomically, this attention network involves portions of the parietal cortex, associated thalamic areas, and parts of the superior colliculus. This "posterior" network is involved in directing attention to relevant locations as in visual search. Three distinct steps are recognised in this process: disengagement of attention from its present focus (parietal cortex), movement of the index of attention to the area of the new target (midbrain), and engaging attention to the new target (thalamus). The basal ganglia have been implicated in the regulation of this orientation of attention (Jackson et al., 1994). A specific pattern of visual attention is apparent after dopaminergic blockade and in patients with PD. PD patients disengaged from attended locations more readily than controls (Wright et al., 1990), implicating interference with the maintenance of attention. This is concordant with studies showing impaired set maintenance in PD (see below).

3.2 Target detection network

A second attention network involves the anterior cingulate gyrus that appears to be active in the conscious detection of events, i.e. the subjective experience of the target. Detection seems to play a role in the production of interference, and thus this system (the anterior network) is active during interference tests such as the Stroop test. The posterior attentional system may modulate activity within the anterior attention system network via the basal ganglia connections with the anterior cingulate gyrus (Jackson et al., 1994). Several studies have confirmed that PD, even early and untreated patients, have less effective mechanisms for resisting interference, leading to difficulties in establishing and maintaining a new response set (Dujardin et al., 1999). It has been suggested, however, that it is not the switching and maintenance of set per se, but rather a general impairment on all cognitive tests which depend on internal cues and strategies, i.e. active, conscious, effort-demanding tasks, whereas performance is normal when external cues (i.e. passive, automatic, unconscious tasks) are provided (Brown & Marsden, 1990). A general theory accounting for these

phenomena is the concept of a "limited-capacity central processor" for performing mental work. The cognitive impairments observed in PD, including deficits in attentional shifts and impairment on effort-demanding tasks, could be explained on the basis of depleted central processing resources. This hypothesis has received some empirical support (Brown & Marsden, 1990). Caudate dopamine depletion may be implicated in these deficits, suggesting that dopaminergic therapy might alleviate this impairment. Indeed, levodopa therapy improves performance on simultaneous cognitive tasks (Malapani et al., 1994), consistent with the hypothesis that adequate dopamine transmission is necessary for normal function of a central processor of mental resources. Levodopa has also been shown to improve executive functions (Lange et al., 1995; Growdon et al., 1998). Most cognitive deficits do not improve after dopaminergic therapy, however, suggesting that non-dopaminergic systems may be more important for these functions.

3.3 Vigilance network

The vigilance system involves locus coeruleus norepinephrine input to the prefrontal cortex. This network is active when subjects are required to maintain the alert state in the foreperiod of a reaction time task when they attend to a source of signal while waiting for an infrequent target to occur (vigilance test). The association of norepinephrine and vigilance in PD was supported in a study finding significant correlations between CSF levels of the norepinephrine metabolite 3-methoxy-4-hydroxyphenethyleneglycol and performance on reaction time and continuous performance tasks (Stern et al., 1984).

3.4 Fluctuating cognition

In 75 hospitalised PD patients with dementia, 46% not receiving anticholinegic drugs and 93% under anticholinergic therapy showed confusional states (defined as acute and reversible impairment of tempero-spatial orientation, inability to act or speak coherently) (de Smet et al., 1982). DLB patients, who share many clinical and pathological features with PD patients, are characterised by marked fluctuations in cognition and consciousness (Walker et al., 2000, see also Chapter 16). Although there are no studies assessing the stability of conscious awareness using adequate methodology in PD, unpublished results from our group suggest that a considerable proportion of demented PD patients show marked fluctuations in their attention and awareness. This similarity among PD and DLB patients suggests that cortical Lewy bodies or

central cholinergic deficits, common in both disorders, may be the underlying cause of these phenomena. This hypothesis has received strong support from case reports and a placebo-controlled study describing marked improvement of attention and wakefulness in DLB patients receiving cholinesterase inhibitors (McKeith et al., 2000). It has been suggested that improved attention and arousal is an important mechanism of the observed improvement after treatment with cholinesterase inhibitors in dementia (Perry et al., 1999). We have recently completed a placebo-controlled study of donepezil in PD patients with dementia showing improvement of general cognition and global functioning (Aarsland, 2001), indicating that cholinergic deficits are of importance in the attentional disturbances of PD patients. Motor fluctuations (alternations between "on"-periods when motor improvement, i.e. striatal dopaminergic transmission is maximal and "off"-periods when motor disability, i.e. striatal dopaminergic transmission is minimal) are common in PD. However, motor fluctuations are not accompanied by significant cognitive or attentional changes (Dubois & Pillon, 1992), suggesting that fluctuation in dopaminergic transmission is not the underlying mechanism of cognitive fluctuations in PD.

4.   Disturbance of cognition: Explicit and implicit memory dysfunction

The distinction between implicit (unconscious) and explicit (conscious) memory refers to the cognitive strategy adopted for retrieval of information, and not to separate memory systems (Schacter & Tulving, 1994). Explicit, or declarative, memory processes include recall, cued recall and recognition, which are at least partially dissociable processes of remembering, but all act to bring memories into consciousness. Implicit, or non-declarative memory includes conditioning, motor learning, habit learning and priming. Amnesic patients usually perform normally on tests of implicit memory, showing that these processes are dissociable from explicit memory, which is severely impaired in amnesia. Explicit memory is thus localised to the limbic-diencephalic structures compromised in the amnesic syndrome.

The learning mechanisms referred to as implicit memory cannot generate conscious recollection, and do not rely on the same neural structures. Classical conditioning of skeletal musculature is dependent on the cerebellum, while emotional conditioning relies on the amygdala and cortical areas for processing. The neural substrate of motor learning is believed to be in the basal ganglia (Heindel et al, 1988, 1989), and this is also, at least partly, true for habit learning or rule learning. The latter are probably also dependent on frontal cortical

structures for execution. Priming is subserved by different cortical processes, dependent on the nature of the priming task (Squire, 1994).

Immediate memory span, semantic recall and naming are generally intact in PD without dementia (Taylor & Saint-Cyr, 1995), as is recognition and cued recall. Encoding, storing and consolidation of new memories also seem to be unaffected (Pillon et al, 1993). Thus memory functions associated with the temporal lobes are usually preserved. Nevertheless, PD patients are impaired in tasks requiring free-recall (Bondi & Kaszniak, 1991), and in semantic fluency tasks, when cues are not provided (Randolph et al, 1993). Generally, PD patients appear to have difficulties in *retrieving* stored information in the absence of external cues, but seem to perform in a normal manner on explicit memory tasks, as long as the task does not require organisation of the material or the generation of strategies for remembering (Pillon et al, 1993).

With the exception of degraded picture identification (Bondi & Kaszniak, 1991), PD patients perform normally on implicit tests of perception, and are only slightly deficient in motor learning tasks (Harrington et al., 1990). Their habit learning skills seem to be more severely compromised (Knowlton et al., 1996).

4.1 The mechanisms of learning and retrieval

Taylor and Saint-Cyr (1995) suggested that PD patients have a core deficit in internalising predictive cues in novel learning situations. They hypothesise that the basal ganglia might be important for "boosting" a correct response, giving it "activational preference" over other responses by inhibiting background activation, and that this might be a function of the "cognitive loop" suggested by Alexander et al. (1986). In a recent review, White (1997) suggested that dopamine is released in response to *new* environmental stimuli or "contexts", thereby reinforcing the creation of a context representation in the basal ganglia. This representation then becomes associated with rules stored in the frontal cortex, and the execution of these rules is dependent on selected output from the basal ganglia. According to White (1997) dopamine is of particular importance in detecting novel or altered contexts. The dopamine depletion in PD might thus prevent the identification and storing of new context representations, which in turn decreases output from the basal ganglia to the frontal lobes, resulting in decreased or deficient rule application.

How this might relate to PD patients' performance on explicit tasks, if at all, is yet not known. A collapse of strategies for explicit retrieval, for voluntarily bringing memories into consciousness, seems to be responsible for the

explicit impairments in PD and this might include an additional deficit in a frontal selection mechanism. The impairments in explicit and implicit memory in PD seem to reflect corresponding underlying deficits, namely a problem in selection or retrieval in the absence of external cues. In other cognitive domains, like naming and reading, increased reliance on external stimuli may be caused by a breakdown in parallel processing and activational feedback from higher levels of processing (Humphreys et al., 1997; Behrmann et al., 1998). If parallel processing and feedback of activation is an attribute of the cortico-striatal loops, as suggested by Alexander et al. (1986) and responses are made by selecting or boosting the most highly activated representation, then a similar model may account for the increased reaction times and deficient learning displayed by PD patients on tests where no cues are given.

4.2 The neurochemistry of retrieval

Explicit memory seems to be unrelated to dopaminergic transmission in PD (Lange et al., 1995; Growdon et al., 1998). Dopaminergic connections may be particularly important in preventing perseveration (Owen et al., 1993), and in rule learning which cannot be conceptualised (like the Tower of Hanoi). An association between cognitive impairment and cortical and hippocampal cholinergic deficits in PD has been found (Kuhl et al., 1996). Consistent with these reports, uncontrolled studies suggest that cholinergic agents may improve memory and other cognitive functions (Hutchinson et al., 1996). In a recent placebo-controlled study of donepezil in PD, MMSE and general cognitive functioning as measured by the clinician improved significantly (Aarsland, 2001). Visual memory and psychomotor speed improved as well, although not significantly. The results strongly suggest that memory, attention and psychomotor speed rely on cholinergic activity in PD patients.

5. Disturbance of perception and thinking: Hallucinations and delusions

In a population-based study, hallucinations had occurred in 16% and delusions in 5% of PD patients during the month prior to evaluation. These symptoms were more common in those with dementia (Aarsland, 1999a). In a recent study using more detailed assessment methods and also including minor forms consisting of a sensation of presence, a sideway passage or illusions, 40%

of PD patients reported having experienced hallucinations during a period of 3 months (Fenelon et al., 2000).

Visual hallucinations are the dominant mode of perceptual disturbances in PD. The most frequent type is presence hallucinations, i.e. a vivid sensation of the presence of someone in the room, followed by passage hallucinations, i.e. brief visions of persons or animals passing sideway. Hallucinations are usually very brief (<5 minutes, commonly a few seconds), and insight into the hallucinatory nature of the phenomena are usually retained in non-demented patients (Fenelon et al., 2000). Twenty-nine percent of demented PD patients had delusions, and the most common delusional ideation were paranoid thinking and phantom boarder phenomenon, i.e. being convinced that there are unwelcomed guests in the house (Aarsland, 2001b). The presentation of hallucinations and delusions is very similar in PD and DLB, and there is a gradient of increasing frequency of hallucinations and delusions in PD without dementia, PD with dementia and DLB. These findings suggest similar underlying mechanisms for hallucinations and delusions in PD and DLB, and adds to the evidence indicating that these two diseases are parts of a continuum of Lewy body disease.

Little is known as to the underlying mechanisms of hallucinations in PD. Although it is usually thought that hallucinations are simply side-effects of dopaminergic agents, reflected in the term "drug-induced hallucinations", a dose-dependent relationship with dopaminergic agents has not been reported (Aarsland et al., 1999a; Fenelon et al., 2000). This does not prove a lack of relationship, since the dosage may have been reduced in patients with hallucinations. However, hallucinations did not relate to plasma levels of levodopa or to sudden changes in plasma levels in a recent experimental study (Goetz et al., 1998). Furthermore, hallucinations were much more common in PD than in patients with progressive supranuclear palsy (PSP) treated with similar doses of dopaminergic agents (Aarsland, 2001d). Thus, non-dopaminergic mechanisms may contribute to hallucinations in PD. Nevertheless, dose reduction of dopaminergic agents may alleviate these symptoms, although formal evaluation of this strategy has not been reported.

Cholinergic deficits are associated with hallucinations in DLB (Perry et al., 1999). Given the similarity found between DLB and PD, it is tempting to hypothesise that cholinergic changes may contribute to hallucinations in PD as well. Preliminary reports showing reduced hallucinations after cholinergic treatment in DLB (Aarsland & Brønnick, 1999c, McKeith et al., 2000) and PD (Hutchinson et al., 1996) support this hypothesis. Cholinergic pontine disturbances may be related to the sleep problems and REM sleep be-

haviour, both related to hallucinations (see below), further supporting the association. Sleep problems, dream phenomena and hallucinations, which occur more commonly in the afternoon and at night (Fenelon et al., 2000), may represent different stages on a continuum of disturbed consciousness (Pappert et al., 1999). In addition, subtle visual impairment may also facilitate visual hallucinations (Diederich et al., 1998). Serotonergic changes may contribute to hallucinations in PD. Increased central serotonergic activity has been found in hallucinating PD patients (Zoldan et al., 1995), and ondansetron, a serotonergic blocking agent, was reported to improve hallucinations (Zoldan et al., 1995). Using atypical antipsychotic agents with low dopamine-blocking activity and relatively high serotonergic blocking activity, hallucinations can be successfully treated (The Parkinson Study Group, 1999).

6.   Disturbance of arousal: Disorders of sleep, dreaming and wakefulness

A wide range of sleep disturbances has been documented in PD (Larsen, 2001). In a population-based survey of sleep disorders in PD, Tandberg et al. (1998) reported nocturnal sleeping problems in 60% of PD patients compared to 33% in healthy controls and 46% in elderly with diabetes mellitus. The most common problem reported was sleep fragmentation, which was found in 39% of PD and only 12% of normal elderly controls, whereas inability to fall asleep did not differ between the groups.

In addition, daytime sleep disorders are common in PD. Mild daytime somnolence and a need for a short nap is common in healthy elderly people. However, Tandberg et al. (1999) reported significantly more excessive daytime sleepiness, (defined as falling asleep three times or more a day or total daytime sleeping more than 2 hours) in PD patients (16%) than healthy elderly controls (1%). This disorder was more common in PD patients with more severe parkinsonism, cognitive impairment and hallucinations.

Sleep attacks, i.e. sudden, irresistible and overwhelming sleepiness, also occurring while driving, have recently been described in PD patients taking dopamine agonists (Ferreira et al., 2000). An interesting parallel exists between the sleep attacks reported in PD and the fluctuating consciousness observed in DLB, where patients may suddenly vary from being mute, confused and unable to stand without assistance to being capable of carrying on a conversation (Walker et al., 2000). The clinical resemblance between these two syndromes suggest possible similar neurochemical substrates.

Other sleep-related phenomena in PD include vivid dreams, altered dream content, night-mares, night-terrors with nocturnal vocalisations, nocturnal hallucinations, somnambulism and REM sleep behaviour disorder (RBD). Polysomnographic sleep studies of PD patients have found decreased total sleep time, decreased sleep efficiency and increased wake time after sleep (Comella et al., 1993). These changes were most prominent in patients with hallucinations, consistent with the clinical descriptions reported above. Hallucinating patients also had reduced REM percentage and REM sleep, whereas non-hallucinators had frequent occurrence of motor activation during REM sleep, i.e. REM sleep behaviour disorder (RBD) (Comella et al., 1993). A causal relationship between reduced REM sleep and hallucinations was suggested in that deprivation of nocturnal REM sleep in PD may cause emergence of REM into the waking state at daytime, which may present as hallucinations (Comella et al., 1993). This hypothesis received support from daytime hallucinations being coincident with REM sleep intrusions in some PD patients (Arnulf et al., 2000). These observations are consistent with previous findings of an association between sleep disturbance, dream phenomena and visual hallucinations in PD (Aarsland 1999; Pappert et al.,1999). RBD may thus arise from the disease itself or may be the effect of dopaminergic therapy. A subsequent report showing that RBD precedes clinical PD by several years and responds to levodopa therapy suggests that RBD is in fact related to the disease and not to the treatment (Tan et al., 1996).

What are the neurochemical and pathological substrates for these disorders in PD? REM sleep is primarily mediated by cholinergic neurones in the pons (Chapters 7 and 8). The pontine tegmental area is involved in the organisation of sleep and projects to the ventromedial reticular formation, which is the main inhibitory centre for REM sleep (Tan et al., 1996). The basal ganglia are interconnected strongly with the pontine tegmental area, and decreased striatal dopaminergic innervation has been found in elderly subjects with chronic idiopathic RBD (Albin et al., 2000). RBD in PD could thus be the result of dysfunction of the pontine tegmental area secondary to basal ganglia dysfunction. Alternatively, RBD could result from primary involvement of the pontine tegmental area in PD patients (Jellinger, 1999). The D1 receptor inhibits REM sleep, and thus the observed improvement of RBD after levodopa-mediated D1 stimulation (Tan et al., 1996) might be caused via D1 mediated reduction of REM sleep.

RBD has also been observed in DLB (Uchiyama et al., 1995; see also Chapter 16) and AD without Lewy bodies (Schenck et al., 1996), associated with neuronal loss in substantia nigra and locus coeruleus in particular. In the AD

case, a higher than expected number of cholinergic mesopontine neurones was found. The noradrenergic locus coeruleus neurones normally inhibit cholinergic mesopontine neurones. Neuronal loss in locus coeruleus is common in PD (Jellinger, 1990). Thus, one alternative mechanism for RBD in PD, and also in AD, is neurone loss or Lewy bodies (Arnulf et al., 2000) in the locus coeruleus, which causes disinhibition of mesopontine cholinergic neurons.

7. Disturbance of motivation and volition: Bradyphrenia and apathy

Bradyphrenia is an important, but poorly defined, concept in the PD literature. It includes slowness of thought, impaired attention and motivation, lack of spontaneity, inflexibility and forgetfulness, and was reported to accompany parkinsonism as far back as 1882 (see Lees, 1994). Severe symptoms may develop: "After a question or command, the verbal or motor response is given after a delay varying from a second or so up to several minutes. The patient may respond to only one question in four or five or ten . . . ." (Fisher, 1983; reviewed in Lees, 1994). However, there are also some reports that PD patients perform as rapidly as control subjects (Duncombe et al., 1994; Phillips et al., 1999), suggesting that the degree of mental slowness may be task-dependent (see above). Although bradyphrenia is said to occur in most PD patients (Lees, 1994), it is more prominent in those with dementia and also with depression. The underlying mechanism is unknown, but seems to be closely related to impairment of dopaminergic transmission (Rogers et al., 1987).

The concept of bradyphrenia overlaps with that of apathy, defined as diminished motivation not attributable to diminished level of consciousness, cognitive impairment or emotional distress (Marin, 1990). Apathy is common in neurodegenerative disorders and is associated with orbito-frontal, medial frontal and anterior temporal dysfunction in Alzheimer's disease (Craig et al., 1996). Apathy is one of the most common neuropsychiatric symptoms in PD, and correlates with executive dysfunction (Aarsland, 1999b). However, apathy is even more common in PSP patients (Aarsland et al., 2001c), possibly related to the more marked involvement of the orbitofrontal and medial frontal circuits in PSP than in PD.

If the hypothesis of a relationship between dopaminergic activity and mental speed is correct, dopaminergic agents should improve cognitive speed. The hypothesis received partial support from studies showing that levodopa may improve arousal, awakening and mood, at least in the initial phase of treatment (Dubois & Pillon, 1992). However, Pillon et al. (1989) did not find such

a relationship, and suggested that non-dopaminergic systems may be related to cognitive speed in PD. Recent evidence from studies in Alzheimer's disease and DLB suggest that cholinergic agents may improve apathy (Kaufer, 1998; McKeith et al., 2000). Whether cholinergic agents could improve apathy and bradyphrenia in PD patients has not been explored yet.

8.   Conclusions

PD patients frequently demonstrate marked alterations of several domains of consciousness including attention, perception, regulation of sleep and arousal and volition as well as the unconscious aspects of memory. These behavioural changes are of major clinical importance for the patients and their care-givers. Although there is much knowledge of the dopaminergic and non-dopaminergic neurochemical changes in PD, the relationship between these changes and the non-motor behavioural alterations are as yet only poorly understood. Further research into these areas will increase the understanding of neurochemical-behavioural relationships, and most importantly, provide leads to future pharmacological treatments of the behavioural symptoms in PD and related disorders.

References

Aarsland, D. et al. (1999a). *Archives of Neurology* 56, 595–601.

Aarsland, D. et al. (1999b). *Journal of Neurology Neurosurgery Psychiatry* 67, 492–496.

Aarsland, D. et al. (1999c). *International Journal of Geriatric Psychiatry* 14, 69–74.

Aarsland, D. et al. (1999d). *International Journal of Geriatric Psychiatry* 14, 866–874.

Aarsland, D. et al. (2000). *Journal of American Geriatric Society* 48, 938–942.

Aarsland, D. et al. (2001a). *Neurology* 56, 730–736.

Aarsland, D. et al. (2001b). *Neurology* 56, Suppl. 3, Ai28.

Aarsland, D. et al. (2001c). *International Journal of Geriatric Psychiatry* 16, 528–536.

Aarsland, D. et al. (2001d). *Journal of Neuropsychiatry and Clinical Neuroscience* 13, 42–49.

Aarsland, D. et al. (2001). Abstract, American Academy of Neurology Meeting, May 2001.

Albin, R.L. et al. (2000). *Neurology* 55, 1400–1412.

Alexander, G.E. et al. (1986). *Annual Review of Neuroscience* 9, 357–381.

Arnulf, I. et al. (2000). *Neurology* 55, 281–288.

Behrmann, M. et al. (1998). *Cognitive Neuropsychology* 15, 7–52.

Bondi, M.W. & A.W. Kaszniak (1991). *Journal of Clinical and Experimental Neuropsychology* 13, 339–358.

Brown, P. & C.D. Marsden (1999). *Lancet* 351, 1801–1804.

Brown, R.G. & C.D. Marsden (1990). *Trends in Neurosciences* 13, 21–29.

Comella, C.L. et al. (1993). *Annals of Neurology* 34, 710–714.

Craig, A.H. et al. (1996). *Archives of Neurology* 53, 1116–1120.

Cummings, J.L. (1993). *Archives of Neurology* 50, 873–880.

de Smet, Y. et al. (1982). *Journal of Neurology, Neurosurgery and Psychiatry* 45, 1161–1164.

Delacourt, J. (1995). *Neuropsychologia* 33, 1061–1074.

Diederich, N. et al. (1998). *Clinical Neuropharmacology* 21, 289–295.

Dubois, B. & B. Pillon (1992). In: S.J. Huber, J.L. Cummings (Eds.), *Parkinson's Disease. Neurobehavioral Aspects* (178–198). New York: Oxford University Press.

Dujardin, K. et al. (1999). *Journal of Neurology* 246, 783–788.

Duncombe, M.E. et al. (1994). *Neuropsychologia* 32, 1383–1396.

Fenelon, G. et al. (2000). *Brain* 123, 733–745.

Ferreira, J.J. et al. (2000). *Lancet* 355, 1333–1334.

Goetz, C.G. et al. (1998). *Neurology* 50, 515–517.

Groenewegen H. (1999). In: E. Wolters, P. Scheltens, H.W. Berendse (Eds.), *Mental Dysfunction in Parkinson's Disease.* Utrecht: The Netherlands. Academic Pharmaceutical Productions, 22–34.

Growdon, J.H. et al. (1998). *Neurology* 50, 1327–1331.

Harrington, D.L. et al. (1990). *Journal of Clinical and Experimental Neuropsychology* 12, 323–339.

Heindel, W.C. et al. (1988). *Behavioural Neuroscience* 102, 141–147.

Heindel, W.C. et al. (1989). *Journal of Neuroscience* 9, 582–587.

Humphreys et al. (1997). *Philosophical Transactions of the Royal Society London (B)*.

Hutchinson, M. & E. Fazzini (1996). *Journal of Neurology, Neurosurgery and Psychiatry* 61, 324–326.

Jackson, S.R. et al. (1994). *Neural Networks* 7, 925–944.

Janvin, C. & D. Aarsland (1999). *Parkinsonism & Related Disorders* 5 (Suppl. 2), 26.

Jellinger, K. (1999). In E. Wolters, P. Scheltens, H.W. Berendse HW (Eds.), *Mental Dysfunction in Parkinson's Disease.* Utrecht, The Netherlands: Academic Pharmaceutical Productions, 82–105.

Kaufer, D. (1998). *Dementia and Geriatric Cognitive Disorders* 9 (Suppl. 2), 8–14.

Kish, S.J. et al. (1988). *New England Journal of Medicine* 318, 786–780.

Knowlton, B.J. et al. (1996). *Science* 273, 1399–1402.

Kuhl, D.E. (1996). *Annals of Neurology* 40, 399–410.

Lange, K.W. et al. (1995). *Journal of Neural Transmission* (Suppl. 46), 423–432.

Larsen, J.P. (2001). *CNS Drugs* 15, 267–275.

Lees, A. (1994). *Review of Neurology, (Paris)* 150, 823–826.

Malapani, C. et al. (1994). *Neurology* 44, 319–326.

Marin, R.S. (1990). *American Journal of Psychiatry* 147, 22–30.

McKeith, I. et al. (2000). *Lancet* 356, 2031–2036.

Owen, A.M. et al. (1993). *Brain* 116, 1159–1175.

Pappert, E.J. et al. (1999). *Movement Disorder* 14, 117–121.

Perry, E. et al. (1993). *Alzheimer's Disease and Associated Disorders* 7, 69–79.

Perry, E. et al. (1999). *Trends in Neurosciences* 22, 273–280.

Phillips, J.G. et al. (1999). *Journal of Gerontology Ageing and Biological Medical Science* 54, M404–M409.

Pillon, B. et al. (1993). *Archives of Neurology* 50, 374–379.

Pillon, B. et al. (1989). *Neurology* 39, 762–768.

Randolph, C. et al. (1993). *Neuropsychology* 7, 82–88.

Rinne, J.O. et al. (2000). *Archives of Neurology* 57, 470–475.

Rogers, D. et al. (1987). *Brain* 110, 761–776.

Schacter, D.L. & E. Tulving (1994). In: D.L. Schacter, E. Tulving (Eds.), *Memory Systems*. Cambridge: MIT Press.

Schenck, C.H. et al. (1996). *Biological Psychiatry* 40, 422–425.

Squire, L.R. (1994). In: D.L. Scahcter, E. Tulving (Eds.), *Memory Systems 1994*. Cambridge: MIT Press.

Starrfelt, R. et al. (2001). Abstract, 7th Nordic Meeting in Neuropsychology.

Stern, Y. et al. (1984). *Archives of Neurology* 41, 1086–1089.

Tan, A. et al. (1996). *Movement Disorders* 11, 214–216.

Tandberg, E. et al. (1998). *Movement Disorders* 13, 895–899.

Tandberg, E. et al (1999). *Movement Disorders* 14, 922–927.

Tandberg, E. et al. (1995). *Movement Disorders* 10, 541–549.

Tandberg, E. et al. (1996). *Archives of Neurology* 53, 175–179.

Taylor, A.E. & J.A. Saint-Cyr (1995). *Brain and Cognition* 28, 281–296.

The Parkinson Study Group (1999). *New England Journal of Medicine* 340, 757–763.

Uchiyama, M. et al. (1995). *Neurology* 45, 709–712.

Walker, M.P. et al. (2000). *Neurology* 54, 1616–1624.

White, N.M. (1997). *Current Opinions in Neurobiology* 7, 164–169.

Wright, M.J. et al. (1990). *Neuropsychologia* 28, 151–159.

Zoldan, J. et al. (1995). *Neurology* 45, 1305–1308.

Dementia with Lewy bodies

A disorder of consciousness?

Matthew Walker and Elaine Perry

1. Introduction

One approach to understanding the human brain is the study of changes in function and behaviour resulting from trauma or disease. Disorders with well-defined pathophysiology provide valuable clinical models of abnormalities of human consciousness and have provided significant advances in determining the neural correlates of consciousness. In particular research in degenerative dementias may provide new insights into neurogenesis of consciousness.

2. Dementia as a disorder of consciousness

Dementia in old age has traditionally been attributed to Alzheimer's disease (AD), vascular dementia (VaD), or a combination of these pathologies. Within the last decade however, advances in immunocytochemical techniques for examining post-mortem brain have identified an additional, common cause of dementia, designated dementia with Lewy bodies (DLB). Dementia with Lewy bodies accounts for 15–20% of late onset dementias, making it the second most common neurodegenerative cause after AD (Gomez-Tortosa et al., 1998; McKeith et al., 1994). Although DLB includes progressive memory loss (Gomez-Tortosa et al., 1998; Kosaka, 1995), it is increasingly being considered in terms of disrupted and abnormal consciousness.

Cortical Lewy body disease produces a clinically distinct dementia syndrome. Two of the three core features of this syndrome involve abnormalities of consciousness, firstly marked fluctuations in consciousness (usually most apparent in applied cognitive performance) and secondly psychosis, in

particular visual hallucinations (the third core feature is the physical symptom of parkinsonism). These abnormalities span two aspects of consciousness; the level of consciousness, pertaining to arousal/activation, and the content of consciousness such as internal percepts. Recent evidence suggests abnormalities in sleep, particularly rapid eye movement (REM) sleep in DLB sufferers are an additional perturbation in consciousness.

In DLB, fluctuations in both the level of consciousness and in the content of consciousness (hallucinations and delusions) develop. These alterations, together with much of the ensuing cognitive impairment, fluctuate to such an extent that patients can transiently return to being symptom-free in the course of the disease. This temporal pattern implicates functional as opposed to structural neuropathological abnormalities in symptom aetiology. Several neurotransmitter correlates have been identified in autopsy tissue from retrospectively, and more recently, prospectively assessed patients.

3. Fluctuating levels of consciousness

3.1 Clinical features

Clinical observations and case reports suggest that fluctuating levels of consciousness (FC) occur in 80-90% of patients with DLB (Byrne et al., 1989; McKeith et al., 1992). In addition, FC occur in 20–25% of patients with AD (Kolbeinsson and Jonsson, 1993; Robertson et al., 1998) and between 35–50% of VaD (Hachinski et al., 1975; Roman et al., 1993) although the periodicity and causality in these dementia subtypes is hypothesized to be different (Walker et al., 2000a). These fluctuations in consciousness are characterized by periodic shifts in the level of arousal ranging from episodes of lucidity to reduced awareness and even stupor.

Striking clinical examples of these fluctuations, together with the ensuing disability, can be found throughout the DLB literature (Ballard et al., 1993; Burkhardt et al., 1988; Gibb et al., 1987; Hely et al., 1996; McKeith et al., 1992; Wagner and Bachman 1996). Furthermore, these fluctuations have been confirmed in the absence of any potential underlying medical cause such as infection or drug intoxication, separating them from delirium.

Although some of the earliest case presentations of cortical Lewy body disease were characterised by "disorientation" (Mitsuyama et al., 1984; Okazaki et al., 1961; Yagishita et al., 1980), the first study to specifically characterise fluctuations was that of Byrne et al. (1989) on 15 DLB cases. For one patient (case 11),

marked fluctuations generated variability in cognitive performance on psychometric testing of more than 50% from one day to the next. In another patient (case 10), fluctuations in consciousness were so catastrophic, that at times the patient was mute, confused and unable to stand without assistance, whilst on other occasions was able to hold a conversation. In a separate study of DLB cases by Gibb and colleagues (Gibb et al., 1987), one patient (case 1) was observed to have episodes of stupor with closed eyes, being difficult to rouse, yet at other times appeared alert and responsive to commands. Similar clinical descriptions of FC were reported by Burkhardt et al. (1988), with patients being described as "fluctuating widely" and suffering "intermittent periods of alertness and also distractibility". McKeith and colleagues, estimated that 86% of DLB sufferers displayed fluctuations, particularly in the level of cognitive impairment, throughout the course of the illness (McKeith et al., 1992), suggesting it was an "essential feature" for a diagnosis of DLB, with "clouding of consciousness" being supportive of DLB. Similar prevalence rates were reflected in studies by Ballard et al. (1993) as well as Geroldi et al. (1997).

More recently, Walker and colleagues characterized FC in dementia using objective psychophysiological measures (Walker et al., 1999; and 2000b). The study cohort, containing both AD and DLB patients as well as matched controls, underwent serial cognitive-attentional reaction time trials and also received repeat examinations of quantitative electroencephalography (EEG). Both the variability in attentional performance and fluctuations in electrocortical arousal significantly correlated with expert clinical ratings of FC, and with each other independently. These data suggest that individuals observed clinically as suffering severe FC display variable attentional performance and express profound fluctuations in electrocortical rhythms on a second to second basis. Such variability in psychological functioning has lead to a cognitive model of FC, indicating that many cognitive faculties, not only attention, are all dependent and hence affected by the stability of consciousness in DLB patients (see Figures 1a and 1b).

3.2 Biological correlates

Fluctuations in the level of attention or conscious awareness are of particular interest in terms of neurochemical correlates, which may in turn help to identify mechanisms involved in maintaining normal levels of consciousness. There is little direct evidence so far concerning which particular neurochemical parameter might be implicated. However, examination of the pathophysiology of DLB suggests potential mechanisms controlling the level of consciousness.
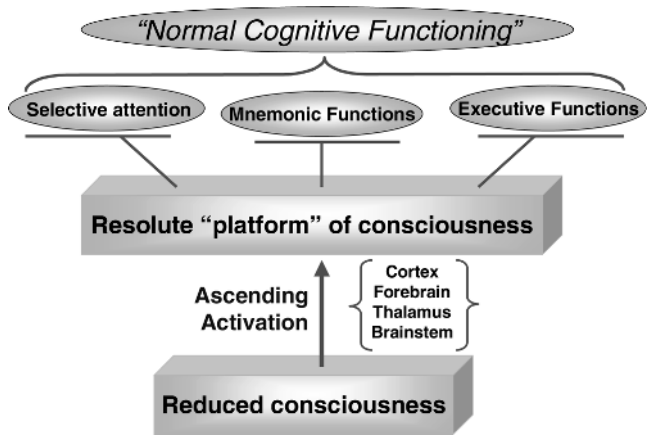
Figure 1a. Ascending activation from subcortical nuclei (see Fig. 2a) generates a stable "platform" of consciousness, essential for normal cognitive functions such as selective attention, learning and memory, and higher executive functions (Walker & Ballard, 1998).
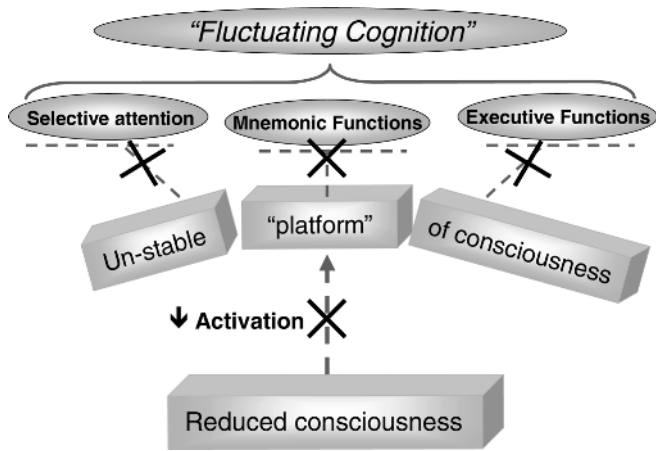
Figure 1b. Dysfunctional consciousness in DLB: reduced ascending activation below an optimal threshold, produces an unstable "platform" of consciousness, resulting in fluctuating cognitive abilities (Walker & Ballard, 1998).

Lewy bodies (LB) are neuronal inclusions, composed of abnormal neuro-filament and synaptic proteins, thought to be surrogate markers for neuronal dysfunction and eventual cell death. They are found in diverse locations including cholinergic and monoaminergic neurons of the brainstem, diencephalon,

basal forebrain (including the nucleus basalis of Meynert), autonomic ganglia and cerebral cortex. However, several lines of evidence suggest LB may not be the direct cause of the disruptions in consciousness in DLB.

The noradrenergic locus coeruleus represents a crucial component of the arousal system (Chapter 3), most evident in the firing patterns across the sleep wake cycle (Kayama & Koyama, 1998). Although the locus coeruleus appears equally affected by cell loss and neurofibrillary tangles (NFT) in AD and LB in DLB (Perry et al., 1990), the prevalence rates of FC in DLB are at least triple those reported in AD. This would suggest that cell loss in the locus coeruleus is unlikely to be the primary cause of FC. The same logic can be extended to the raphé nuclei since these cells groups are also affected by NFT in AD and LB in DLB. However, there may be distinctions between AD and DLB on the basis of pathology in the pedunculopontine (PPT) and laterodorsal (LDT) tegmental brainstem nuclei. Both these cholinergic groups are critical components of the ascending reticular activating system (ARAS). Furthermore, they also extensively innervate the thalamus and basal forebrain regions, the circuitry of which has been implicated in the generation, maintenance and modulation of consciousness (Chapter 2). Whilst pathology in these nuclei in DLB is indicated by several case reports of brainstem LB (Burkhardt et al., 1988; Halliday et al., 1997; Uchiyama et al., 1995; Yamamoto & Imai, 1988), systematic pathological assessments have not yet been made.

Nuclei of the ARAS stimulate the cortex by way of ventral projections to the basal forebrain, in addition to the more dorsal innervation of the thalamus. Integrity of the forebrain bundle is crucial for maintenance of arousal levels (Szymusiak, 1995; Casamenti et al., 1986; Biesold et al., 1989; Adachi et al., 1990). Neuronal loss in the basal forebrain, particularly the cholinergic nucleus basalis of Meynert (NbM), is a pathological feature of DLB, although there are some reports of severe neuronal loss in AD (for review see Mesulam, 1996). However, in a comparative investigation, Lippa and colleagues (1999) identified significantly greater reductions of neuronal numbers in the NbM in DLB compared with AD cases and controls. These observations indicate that whilst AD is primarily associated with dysfunction of cholinergic axonal input to the cortex, DLB is more likely to involve degeneration of the basal forebrain cholinergic system. Hence, despite NbM pathology in both AD and DLB, there is evidence to suggest a greater damage to this forebrain region in DLB. If correct, this would predispose DLB patients to experience even greater reductions, if not fluctuations, in the level of consciousness than AD patients.

Although early structural changes outlined above could result in variable nerve cell activity, the end stage (neuronal loss) is permanent in these brain areas. Structural deficits could thus account for prolonged reductions in the level of consciousness in DLB sufferers, although perhaps not the rapid second to second fluctuations that have been identified using psychometric tests. In contrast however, deficits in neural transmission and receptor interaction may have a greater potential to generate fluctuating consciousness as in DLB. A robust neurochemical correlate of DLB is an extensive cholinergic dysfunction in subcortical and neocortical areas.

Perry et al. (1995) described extensive reductions in nicotinic binding throughout brainstem lateral tegmental regions in patients with DLB compared to elderly controls. This region, rich in cholinergic perikarya, sends activating input to the cortex and appears to be regulated in part by the neurochemical adenosine (Portas et al., 1997). Increases in extracellular adenosine concentration decrease the activity of these wakefulness-promoting cholinergic cell groups, forming an important ultradian homeostatic feedback regulator of conscious level. Therefore, dysfunctional nicotinic regulation at this caudal activating center may be associated with variable ascending impulses to the cortex as well as a loss of normal wake promoting regulation across the day.

In addition to innervation of the basal forebrain from the reticular core, other subcortical systems facilitate basal forebrain activity, including the basal ganglia, locus coeruleus and raphé nuclei (Sarter and Bruno, 1999). The ability of the forebrain to express fast coherent EEG activity of the type associated with awareness and conscious perception (Pare and Llinas, 1995) has been shown to rely upon aminergic neurotransmitters (Cape and Jones, 1998). These aminergic cell groups, know to innervate the NbM (Sarter and Bruno, 1999), are severely reduced in DLB, including dopaminergic contributions from the basal ganglia (Double et al., 1996; Perry et al., 1990b) and noradrenergic and seretonergic brainstem neurons (Perry, 1990a). These findings indicate that, in addition to pathology of cholinergic NbM, modulatory systems that help maintain the stable control of cortical arousal via the basal forebrain are also compromised in DLB.

Among subcortical structures controlling the level of arousal, it is probably the thalamus that is most established in the regulation of conscious level, especially considering its anatomical connectivity and functional properties (for reviews see Newman, 1995). Several theories of consciousness have focused on the thalamic reticular nucleus (e.g. Crick, 1984), a sheet of GABAergic cells that surround the sensory thalamic core. The reticular nucleus, receiving topographical input from the entire cortex, regulates output from almost all other

thalamic nuclei, indirectly controlling the thalamic oscillatory activation to and from the cortex (Steriade, 2000). High affinity nicotinic receptors are reduced in the thalamic reticular nucleus in DLB cases (Spurden et al., 1997), along with a significant decline in alpha-bungarotoxin binding to the α7 nicotinic receptor (Court et al., 1999). These cholinergic receptor abnormalities presumably alter the sensitivity of the thalamus to incoming impulses from the ARAS and descending relays from the cortex. It may be this deficit of thalamic nicotinic receptors that represents one of the strongest candidates generating variable oscillatory activation of the cortex, and explains the gross fluctuations in electrocortical patterns and variability in attentional test performance in DLB patients (Walker et al., 2000a).

Ballard et al. (in prep) examined potential associations between muscarinic and nicotinic receptor subtypes and FC in a prospective clinical study of DLB patients followed to post-mortem. Interestingly only nicotinic binding of epibatidine (α3 and α4 / β2 nicotinic receptors), which was lower than in controls, was found to be significantly higher in the temporal cortex of patients with FC compared to those without, suggesting that this class of receptor has an important involvement in the generation of FC in DLB. Although higher receptor density associated with FC appears counterintuitive, there is immunocytochemical evidence that cortical nicotinic receptors are associated with both GABAergic interneurones (Alkondon and Albuquerque, 1995; Alkondon et al., 1997) and other excitatory and modulatory transmitter systems. The 'balance' of remaining nicotinic receptors in the cortex of DLB patients experiencing FC therefore appears to be changed, perhaps with a greater proportion of receptors being sited on inhibitory neurons causing functional instability. This could lead to oscillations in the magnitude of cholinergic transmission and hence in levels of attention/consciousness, as observed in DLB patients with FC (Walker et al., 2000a).

Interestingly, besides the direct excitatory inputs to the cortex from the basal forebrain, cholinergic NbM neurons may also alter cortical arousal by indirect inhibitory projections to the thalamic reticular nucleus (Parent et al., 1996). Since these neurons together with their receptors at the reticular nucleus are severely affected in DLB, this indirect regulatory pathway should also be recognized as being potentially involved in the generation of FC through a loss of inhibitory cholinergic NbM control of the reticular nucleus.

In summary therefore, it would appear that that the pathophysiology of DLB predisposes patients to not only reductions in the basic level of arousal due to a loss of ascending cholinergic activation, but also fluctuations in the level of arousal, most likely due to abnormalities at the reticular nucleus of the

thalamus and at the cortex. A summary model of these biological abnormalities and their contribution to FC is provided in Figures 2a and 2b. Preliminary clinical studies have indicated the potential of cholinergic therapy in normalizing these fluctuations in DLB patients, providing validation to this model. Kaufer et al. (1998) reported two DLB patients who experienced marked improvement of FC in response to donepezil, a cholinesterase-inhibitor. Consistent with this, in a double blind placebo controlled trial, 102 DLB patients were randomized to treatment with the cholinesterase inhibitor rivastigmine

Neuronal systems implicated in regulating consciousness

By receiving consistent activation from both thalamic sensory relay and basal forebrain activation, the cortex can maintain a "stable" level of consciousness.

The GABAergic reticular nucleus of the thalamus "gates" sensory information transfer from the thalamus to the cortex.

The cholinergic basal forebrain receives and translates varied sub cortical inputs into neocortical activation.

Afferent cholinergic projections from the ascending reticular activating system to the thalamus (dorsal stream) and to the forebrain (ventral stream).

Figure 2a. Systems implicated in regulating the level of consciousness: afferent projections from the ascending reticular activating system (ARAS), predominantly cholinergic from the pedunculopontine tegmental nuclei (PPT) and laterodorsal tegmental nuclei (LDT), innervate both the GABA-ergic reticular nucleus (RtN) and sensory thalamic relay nuclei (dorsal pathway) as well as the basal forebrain (ventral pathway). Brainstem cholinergic projections inhibit the Rtn of the thalamus, allowing thalamic relay neurons to transmit sensory input to the cortex. Ventrally projecting brainstem cholinergic systems, together with heterogeneous subcortical inputs to the basal forebrain (particularly the nucleus basalis of Meynert) result in extensive cholinergic excitation of the cortex, propagating cerebral activity, in unison with thalamic innervation. The hypothesized consequence of these modulatory systems is the maintenance of cortical activation providing a stable level of consciousness.

or placebo for 20 weeks. Patients receiving the cholinesterase inhibitor had significantly less fluctuating confusion on an informant rated diary (McKeith et al., 2000a) and significantly less fluctuation in attentional performance (Ballard et al., 2000a); both symptoms closely associated with FC (Walker et al., 2000a; Walker et al., 2000b).

Pathophysiological model of fluctuating levels of consciousness
(Based on the pathophysiology of dementia with Lewy bodies)

The cortex suffers reduced and sporadic activation from subcortical activators resulting in fluctuating consciousness.

Cholinergic receptor alterations at the reticular nucleus prevent stable "gating" of information to and from the cortex.

Pathological changes in the basal forebrain, and the inputs it receives (aminergic), and sends compromise cortical cholinergic activation

Disruptions to the cholinergic tegmental nuclei reduce output to both the dorsal (thalamus) and ventral (basal forebrain) pathways.

= Areas of know pathophysiology

Figure 2b. Proposed pathophysiological model of fluctuating levels of consciousness: Loss of afferent projections from the ascending reticular activating system (ARAS) reduces the control of cholinergic innervation at the reticular nucleus (RtN) and sensory thalamic relay nuclei (dorsal pathway), and at the site of the basal forebrain (ventral pathway). Nicotinic receptor alterations at the RtN generate unstable "gating" of afferent sensory information to the cortex. Reductions in cholinergic facilitation of the thalamic sensory relay nuclei also reduce the efficiency of the dorsal projections to the cortex. Pathophysiological cholinergic deficits at the level of the basal forebrain, combined with reduced brainstem and aminergic innervation, give rise to extensive loss of normal forebrain cholinergic facilitation to the cortex. Diminished ventral and dorsal-pathway facilitation, combined with neocortical cholinergic compromise, may therefore lead to disintegration of stable cerebral activation, resulting in significant fluctuations in the level of consciousness.

4.   Psychosis

4.1 Clinical symptoms

Psychotic symptoms, particularly hallucinations (predominantly visual and to a lesser extent auditory), are common in DLB. Prevalence rates have varied from between 13% (Byrne et al., 1989) and 80% (McKeith et al., 1992). However, these discrepant figures may reflect the specialty setting of the clinical populations; lower prevalence rates being associated with neurological services compared with psychiatric services.

Characteristically the visual hallucinations in DLB consist of complete, detailed images, normal in size and tending to move, many containing people or animals. These descriptions are similar to visual hallucinations experienced by patients with other conditions including PD (Cummings & Benson, 1992) and the Charles Bonnet Syndrome (Manford & Andermann, 1998). Patients with DLB are also more likely to continue to have visual hallucinations during the duration of their illness than patients with AD (Ballard et al., 1998).

In addition to prominent and persistent hallucinations, delusions and delusional misidentifications occur in over half of DLB patients (Ballard and Oyebode, 1995; Ballard et al., 1999), more commonly than in AD (Ballard et al., 1999). These delusions are defined as persistent false unshakeable beliefs, which cannot be understood in terms of the individual's peer group or culture, and are generally of a paranoid nature.

4.2 Biological correlates

In an early retrospective analysis of DLB cases, patients with hallucinations were found to have lower cholinergic activity in temporal and parietal cortex (assessed on the basis of ChAT levels) than those without hallucinations (Perry et al., 1990a). There was also evidence of a serotonergic: cholinergic imbalance based on relatively higher 5HT turnover in the hallucinators. In a prospectively assessed cohort, the relationship with lower neocortical ChAT has been confirmed (Ballard et al., 2000b) and in addition low affinity nicotinic receptors (binding α-bungarotoxin) but not high affinity nicotinic or muscarinic M1 receptors, were lower in temporal association cortex in hallucinators (Ballard et al., in preparation). The implications of cholinergic dysfunction is consistent with psychopharmacological evidence that anticholinergic drugs induce similar types of hallucinations in normal individuals (Chapters 12 and 13) and with clinical trials of cholinesterase inhibition in DLB patients in which hallu-

cinations are significantly reduced (McKeith et al., 2000b). It will be interesting to establish if such treatment restores the hypometabolism in occipital cortex (primary visual area) identified in hallucinating DLB patients (Imamura et al., 1999). There is a relatively high density of M1 muscarinic receptors in human visual cortex (Chapter 13). Mori et al. (2000) suggest that defective visual perception in DLB contributes to visual hallucinations, delusional misidentification and visual agnosias.

The evidence for an involvement of the low affinity nicotinic receptor subtype (α-7) suggests that clinical effects of nicotinic agonists, or drugs like galantimine with nicotinic actions, should be evaluated, although there is as yet no evidence that nicotinic antagonists induce hallucinations. The α-7 nicotinic receptor has also been found to be lower in patients experiencing delusional misidentification (including the Capgras phenomenon as well as misinterpretation, of television and photograph images), compared to patients without this symptom (Ballard et al., in preparation).

While dopaminergic and 5-HT pre-synaptic transporter activities and D1 or D2 receptors did not distinguish DLB patients with hallucinations or delusional misidentification, in those experiencing auditory hallucinations D2 receptor binding was in temporal association cortex relatively higher in those affected with this symptom (Piggott et al., submitted). There are some similarities between the nature of auditory hallucinations in dementia syndromes such as DLB and schizophrenia, including the experiences of voices in the second person, although in schizophrenia third person auditory hallucinations are common. Dopaminergic hyperactivity is considered to underpin such key symptoms in schizophrenia (Chapter 17). No other dopaminergic or cholinergic neurochemical parameter so far examined in DLB has been found to correlate with auditory hallucinations. Whether neuroleptics, which target D2 receptors, specifically ameliorate this symptom in DLB (affecting one third of patients) as they do in schizophrenia, has not yet been evaluated, although neuroleptic sensitivity in DLB is problematic.

As well as the hallucinatory psychosis in DLB, delusional episodes are also present. In a recent prospective clinical study, deluded DLB patients were distinguished from non-deluded by higher muscarinic M1 receptor binding in temporal cortex (Ballard et al., 2000b). Muscarinic M1 receptors are elevated overall in DLB (Perry et al., 1990a; Shiozaki et al., 1999) probably in response to diminished pre-synaptic cholinergic activity, although how the extent of this upregulation relates to delusional symptomatology is unclear. Delusions in DLB are nevertheless diminished as a result of chronic rivastigmine administration (McKeith et al., 2000b). It is likely, though no evidence is yet available,

that elevating levels of acetylcholine will be associated with normalization of M1 receptor levels.

5. Sleep abnormalities in DLB

Increasing evidence indicates that patients with DLB experience changes in sleep behaviour and sleep architecture, both of which add to carer burden and may lead to prescription of additional medication. Sleep in DLB has not been as extensively investigated as in AD in which reductions in REM sleep (Ancoli-Israel et al., 1994) nocturnal wandering and confusion (Ancoli-Israel et al., 1994) and sleep apnoea have been documented (Bader et al., 1996). In DLB however, the most common sleep abnormality reported to date has been a loss of the muscle paralysis associated with REM sleep periods. This REM sleep behaviour disorder (RBD) represents a form of dissociated conscious state associated with the "acting out" of dreams (Schenck et al., 1997). The ultradian cycle of NREM and REM sleep throughout the night is strictly controlled by the brainstem neuronal populations of the locus coeruleus, raphe nuclei and tegmental nuclei (Hobson et al., 1975). Normal REM sleep is characterized by muscle atonia particularly affecting the antigravity muscles and is initiated by cholinergic brainstem neurons.

Several reports have identified RBD in DLB sufferers (Boeve et al., 1998; Ferman et al., 1999; Schenck et al., 1997; Turner et al., 1997; Uchiyama et al., 1995). In one case report, the symptoms of RBD presented 17 years before the diagnosis of DLB was made (Turner et al., 1997). Uchiyama et al. (1995) have also identified RBD in a patient with a 20-year history of nocturnal violent behavior during sleep. In this case, histopathologic examination at post-mortem confirmed the diagnosis of DLB together with a marked decrease of pigmented neurons in the locus coeruleus and substantia nigra. It has been hypothesized that Lewy body pathology in the locus coeruleus prevents the normal noradrenergic inhibition of cholinergic tegmental brainstem populations resulting in REM sleep abnormalities, particularly RBD (Turner et al., 2000). If this pattern of preceding RBD is consistent, then its occurrence may serve as an early clinical indication for those at risk of progressive neurodegenerative disorders, particularly DLB.

Grace and collegues (2000) have recently utilized structured sleep questionnaires to assess the frequency of sleep disturbances in patients with DLB and AD. The scales were repeated in a subgroup of these patients after treatment with the cholinesterase inhibitor rivastigmine. DLB patients had more

overall sleep disturbance, more movement disorders whilst asleep, more unpleasant dreams and confusion on waking as well as more abnormal daytime sleepiness. Treatment with rivastigmine produced a trend towards normalization of sleep profiles in the small number of subjects followed up. These data not only reemphasize the value of sleep investigations in the differential diagnosis of dementia, but also suggest a neurochemical cholinergic correlate as a potential underlying cause.

REM sleep changes may be related to the high prevalence of hallucinosis in DLB sufferers. Disrupted sleep patterns in narcolepsy and delirium tremens are believed to trigger hallucinatory REM sleep like intrusions in the waking period, the so-called "REM-rebound" effect (Aldrich, 1992; Lishman, 1987). A similar pattern of fragmented REM sleep could predispose DLB patients to a high REM sleep pressure, which intrudes into the wake state in the form of visual and auditory hallucinations, much like that hypothesized in PD patients (Arnulf et al., 2000). Indeed, Comella et al. (1993) demonstrated that hallucinating PD patients exhibit 75% less REM sleep and take twice as long to achieve the first REM stage than non-hallucinating PD cases, and concluded that a sleep-rebound effect (mainly REM) was the cause of psychosis in these patients. Whilst large prospective sleep profiling has not yet been undertaken in DLB subjects, it is clear that REM sleep and the brainstem mechanisms which govern the associated muscle atonia are impaired in these patients. It is possible that the high prevalence of visual and auditory hallucinations seen in DLB coincides with daytime episodes of REM sleep and may be the consequence of dream intrusions (Arnulf et al., 2000).

Existing data therefore suggest that sufferers of DLB may experience a breakdown in the regulation of the principal components of REM sleep: dreaming, atonia and sleep structure itself. Dedicated electrophysiological recordings of sleep architecture throughout the night, and day time EEG changes event related to the appearance of hallucinations, delusions and fluctuations in consciousness, together with pathological follow-ups are required for confirmation of these hypotheses.

6.   Conclusions

The increasingly well-defined pathophysiology of the degenerative dementias adds a new domain to our understanding of the neural substrates of consciousness. The syndrome of dementia with Lewy bodies is distinguished by severe disturbances in consciousness. Patients with DLB suffer not only fluctuations

in the level of conscious, but also abnormalities in the content and quality of consciousness such as hallucinations, delusions and sleep disorders. Since neuropathological features of DLB such as Lewy body density correlate only weakly with clinical symptoms (Gomez-Tortosa et al., 1999), neurochemical correlates as identified above are likely to be important in explaining the origins of symptoms that involve altered conscious awareness and in their treatment. While much more research is needed, including functional imaging in vivo and more thorough investigation of sleep abnormalities, the data so far available suggest these disturbances in consciousness are due in large part to cholinergic abnormalities and are amenable to treatment.

References

Adachi, T. et al. (1990). *Brain Research* 514, 163–166.

Aldrich, M. (1992). *Neurology* 42, 34–43.

Alkondon, M. & E. Albuquerque (1995). *Journal of Pharmacology and Experimental Therapy* 274, 771–782.

Alkondon, M. et al. (1997). *Journal of Pharmacology and Experimental Therapy* 283, 1396–1411.

Ancoli-Israel, S. et al. (1994). *Aging Clinical & Experimental Research* 6, 451–458.

Arnulf, I. et al. (2000). *Neurology* 55, 281–288.

Bader, G.G. et al. (1996). *Dementia* 7, 279–287.

Ballard, C. & F. Oyebode (1995). *International Journal of Geriatric Psychiatry* 10, 743–752.

Ballard, C. et al. (1999). *American Journal of Psychiatry* 156, 1039–1045.

Ballard, C.G. et al. (1993). *International Journal of Geriatric Psychiatry* 8, 571–576.

Ballard, C.G. et al. (1998). *Age & Ageing* 27, 631–636.

Ballard, C.G. et al. (2000a). *Neurology* 54(suppl 3), A451.

Ballard, CG. et al. (2000b). *Annals of Neurology*. In press.

Biesold, D. et al. (1989). *Neuroscience Letters* 98, 39–44.

Boeve, B. et al. (1998). *Neurology* 51, 363–370.

Burkhardt, C.R. et al. (1998). 38, 1520–1528.

Byrne, E.J. et al. (1989). *Journal of Neurology, Neurosurgery & Psychiatry* 52, 709–717.

Cape, E.G. & B.E. Jones (1998). *Journal of Neuroscience* 18, 2653–2666.

Casamenti, F. et al. (1986). *Brain Research Bulletin* 16, 689–695.

Comella, C. et al. (1993). *Annals of Neurology* 34, 710–714.

Court, J. et al. (1999). *Journal of Neurochemistry* 73, 1590–1597.

Crick, F. (1984). *Proceedings of the National Academy of Science USA, 81*, 4586–4590.

Cummings, J.L. & D.F. Benson (1992). Dementia: A Clinical Approach. Boston: Butterworth–Heineman.

Dickson, D.W. et al. (1987). *Acta Neuropathology* 75, 8–15.

Double, K.I. et al. (1996). *Dementia* 7, 304–313.

Ferman, T. et al. (1999). *Neurology* 52, 951–957.

Geroldi, C. et al. (1997). *Dementia & Geriatric Cognitive Disorders* 8, 188–197.

Gibb, W.R.G. et al. (1987). *Brain* 110, 1131–1153.

Gomez-Tortosa, E. et al. (1998). *Journal of the American Geriatrics Society* 46, 1449–1458.

Gomez-Tortosa, E. et al. (1999). *Neurology* 53, 1284–1291.

Grace, J. et al. (2000). *International Journal of Geriatric Psychiatry* 15, 1028–1033.

Hachinski, V.C. et al. (1975). *Archives of Neurology* 32, 632–637.

Halliday, G. et al. (1997). *Neuroscience Letters* 227, 49–52.

Hely, M.A. et al. (1996). *Journal of Neurology, Neurosurgery & Psychiatry* 60, 531–538.

Hobson, J.A. et al. (1975). *Science* 189, 55–58.

Imamura, T. et al. (2000). *European Journal of Neurology* 7, 77–79.

Jones, B. & A.C. Cuello (1989). *Neuroscience* 31, 37–61.

Kaufer, D.I. et al. (1998). *Neurology* 51, 1512.

Kayama, Y. & Y. Koyama (1998). *European Urology* 33(suppl. 3), 12–15.

Kolbeinsson, H. & A. Jonsson (1993). *Acta Psychiatrica Scandinavica* 87, 123–127.

Kosaka, K. (1995). *Clinical Neurology* 35, 1455–1456.

Langlais, P.J. et al. (1993). *Neurology* 43, 1927–1934.

Lippa, C.F. et al. (1999). *Journal of Neural Transmission* 106, 525–535.

Lishman, W. (1987). In W.A. Lishman (Ed.), *Organic Psychiatry*, 3rd ed., pp. 594–609. Blackwell Scientific Publications.

Manford, M. & F. Andermann (1998). *Brain* 121, 819–840.

McKeith, I.G. et al. (2000a). *Neurology* 54(suppl 3), A450.

McKeith, I.G. et al. (1994). *Neurology* 44, 872–877.

McKeith, I.G. et al. (1992). *Psychological Medicine* 22, 911–922.

McKeith, I.G. et al. (2000b). *International Journal of Geriatric Psychiatry* 15, 387–392.

Mesulam, M.M. (1996). *Progress in Brain Research* 109, 285–297.

Mitsuyama, Y. et al. (1984). *Folia Psychiatrica et Neurologica Japonica* 38, 81–88.

Mori, E. et al. (2000). *Archives of Neurology* 57, 489–493.

Newman, J. (1995). *Conscious Cognition* 4, 172–193.

Okazaki, H. et al. (1961). *Journal of Neuropathology and Experimental Neurology* 20, 237–244.

Pare, D. & R. Llinas (1995). *Neuropsychologia* 33, 1155–1168.

Parent, A. et al. (1988). *Journal of Compative Neurology* 277, 281–301.

Perry, E.K. et al. (1990a). *Journal of Neurochemistry* 55, 1454–1456.

Perry, E.K. et al. (1990b). *Alzheimer Disease and Associated Disorders* 4, 87–95.

Perry, E.K. & R.H. Perry (1993). *International Review of Psychiatry* 5, 363–380.

Perry, E.K. & R.H. Perry (1995). *Brain & Cognition* 28, 240–258.

Perry, E.K. et al. (1999). *Trends in Neuroscience* 22, 273–280.

Perry, E.K. et al. (1995). *Neuroscience* 64, 385–395.

Perry, R.H. et al. (1990). *Journal of Neurological Sciences* 95, 119–135.

Piggott, M. et al. (submitted). *Brain.*

Portas, C.M. et al. (1997). *Neuroscience* 79, 225–235.

Robertson, B. et al. (1998). *International Journal of Geriatric Psychiatry* 13, 49–56.

Roman, G.C. et al. (1993). *Neurology* 43, 250–260.

Sarter, M. & J.P. Bruno (1999). *Trends in Neurosciences* 22, 67–74.

Schenck, C. et al. (1997). *Biological Psychiatry* 42, 527–528.

Shiozaki, K. et al. (1999). *Journal of Neurology, Neurosurgery and Psychiatry* 67, 209–213.

Spurden, D.P. et al. (1997). *Journal of Chemical Neuroanatomy* 13, 105–113.

Steriade, M. et al. (2000). *Neuroscience* 101, 243–276.

Szymusiak, R. et al. (1995). *Sleep* 18, 478–500.

Turner, R. et al. (1997). *Neurology* 49, 523–527.

Turner, R.S.D. et al. (2000). *Neurology* 55, 1730–1732.

Uchiyama, M. et al. (1995). *Neurology* 45, 709–712.

Wagner, M.T. & D.L. Bachman (1996). *Archives of Clinical Neuropsychology* 11, 175–184.

Walker, M.P. & C.G. Ballard *CNS* 47, 1113–1124.

Walker, M.P. et al. (1999). *Human Psychopharmacology* 14, 483–489.

Walker, M.P. et al. (2000a). *Neurology* 54, 1616–1625.

Walker, M.P. et al. (2000b). *British Journal of Psychiatry* 177, 252–256.

Yagishita, S. et al. (1980). *Acta Neuropathologica* 49, 187–191.

Yamamoto, T. & T.A. Imai (1988). *Journal of Neuropathology and Experimental Neurology* 47, 536–548.

CHAPTER 17

Schizophrenia

Gavin P. Reynolds

1.   Introduction

The neurochemistry of schizophrenia has been considered in a variety of ways by numerous investigators and most have, as here, focussed on the role of abnormalities and/or dysfunction of brain neurotransmitter systems in the disease. Implicit in a book on the neurochemistry of consciousness is the assumption that this chapter will address the neurochemical basis of the disturbance(s) of consciousness that occurs in schizophrenia. Consciousness in its particular and generally-understood meaning is not obviously distorted in schizophrenia, although schizophrenic patients clearly have a different, or abnormal experience of the external world—their conscious awareness is disturbed.

There are many facets to the disturbance of conscious awareness in schizophrenia. Underlying the positive symptoms is a distorted perception of reality which, in the case of hallucinations, results in a misinterpretation of internally-generated experience (e.g. thought) as externally-originating (reality). Frith (1992) proposes this to be a disorder of self-monitoring, while a disorder of monitoring the intentions of others results in delusions. The negative signs of schizophrenia do not so directly relate to a disturbance of conscious awareness, although the poverty of movement and affect may appear, probably misleadingly, to relate to a diminished awareness of the immediate environment. However, there are also impairments of attention and memory, components of the cognitive deficit of the disease. This third set of disease features, considered to be distinct from the negative symptoms, are only now beginning to be recognised as a target for drug treatment; classical and newer antipsychotic drugs have little effect on cognitive function in schizophrenia.

This is but one classification of symptoms and signs in schizophrenia, representing a natural progression from the positive-negative dichotomy with its proposed pathogenic correlates (Crow, 1985). Other approaches include that of

Liddle et al. (1992) who identified three syndromes described as "psychomotor poverty," "disorganization" and "reality distortion" on the basis of symptom cluster correlates. Each of these syndromes has a specific pattern of abnormality in regional cerebral blood flow—a measure of neuronal activity—as determined by neuroimaging. From a neuroscientific perspective, this has the advantage of having neuroanatomical correlates, although the pathological changes underlying these abnormalities of brain activity remain undefined.

There is a huge body of neurochemical evidence indicating disturbances of various neurotransmitter systems in schizophrenia, which have been comprehensively reviewed elsewhere (e.g. Reynolds, 1995; Owen & Simpson, 1995). Few, if any, studies have successfully determined the relationships of neurochemical or histopathological abnormalities with specific syndromes or symptoms in schizophrenia. This is not surprising considering the limitations associated with neurochemical pathological studies of brain disease, most of which, at least until recently, have relied on the post mortem study of brain tissue. Post-mortem neurochemistry has certainly contributed hugely to our understanding of neurological and psychiatric disease, no more so than in the case of Parkinson's disease in which the identified dopamine deficits led directly to the development of l-dopa treatment. However, such studies rely on a resource—post-mortem brain tissue from clearly diagnosed subjects—that requires substantial effort and cooperation to obtain, and which has its own particular limitations relating *inter alia* to the availability and choice of control samples and the effects of prior drug treatment and agonal state. These limitations can be avoided by modern functional imaging techniques such as fMRI, MRS, PET and SPECT, which offer the opportunity to assess neuronal activity and neurochemical processes *in vivo*, and which have begun to identify pathologies of transmitter release and receptor density in schizophrenia.

2.   Early neurochemical theories

Neurochemical approaches to the understanding of brain dysfunction in schizophrenia started from the assumption that there must be an underlying disturbance of brain biochemistry. This originated from the observation that psychosis in humans, and equivalent bizarre behaviours in animals, could be induced by certain drugs, and these psychotogenic drugs had biochemical and pharmacological effects that may mimic the disturbance in schizophrenia. Two overlapping hypotheses that drove neurochemical research into schizophre-

nia in the early 1950's were the transmethylation hypothesis and the serotonin deficiency hypothesis.

The transmethylation hypothesis depended on the "psychosis" of mescaline as an example of how methylated compounds similar in structure to the monoamine neurotransmitters could be psychotogenic, and demonstrated how methionine, the precursor of the methyl donor S-adenosylmethionine, could exacerbate the psychotic symptoms of schizophrenia in patients. This theory was fed by studies of the now notorious "pink spot," an amine found in paper chromatography of urine extracts from schizophrenics and thought to be 3,4-dimethoxyphenylethylamine (i.e., O-methylated dopamine). Subsequent studies eventually identified this as another compound or compounds, primarily of dietary origin. Another methylated derivative erroneously proposed to be found in higher quantities in schizophrenia was dimethyltryptamine. This compound is similar in structure to LSD, the hallucinogenic nature of which was the key to the serotonin deficiency hypothesis, which proposed that the known antagonism of serotonin (5-HT) by LSD indicated that psychotic disorders such as schizophrenia may result from a hypofunction of 5-HT.

Several limitations of these hypotheses are easy to identify in retrospect. They relied mainly on the psychosis induced by psychotogenic drugs as a model for schizophrenia. This is, however, a poor model; LSD for example produces distortions of reality and visual hallucinations that are rarely found in schizophrenia, in which auditory hallucinations are far more common. No understanding of the negative and cognitive symptoms of schizophrenia was provided, perhaps a reflection of the emphasis being placed at the time on Schneider's first rank symptoms. Nevertheless, there remains some interest in the possible role of 5-HT systems in schizophrenia, partly driven by the fact that the 5-HT2 receptor antagonism demonstrated by most of the newer antipsychotic drugs is considered by some to be an important contributor to their efficacy. Some of the changes reported in 5-HT receptors may reflect the neuronal pathology of the disease (see below), although the finding of 5-HT uptake site deficits in the frontal cortex (e.g. Joyce et al., 1993) may indicate abnormalities of serotonergic innervation that have yet to be fully investigated.

The 1960's and 1970's saw several other hypotheses proposed and disproven. The monoamine oxidase (MAO) deficiency hypothesis was based on the observation of diminished activity of platelet MAO-B in schizophrenia, although this was likely to be an artifact of drug treatment and the small deficits could not, in any case, account for changes in monoamine transmitters. Other hypotheses relating to, among other transmitter molecules, noradrenaline and enkephalin/endorphin have also been proposed. Each of these have had propo-

nents arguing for either increases or for decreases in schizophrenia, depending on how the limited supporting evidence was interpreted.

3.   The dopamine hypothesis

3.1   Dopamine receptors

Providing a island of relative rationality in this sea of speculation has been the dopamine hypothesis. First based on the effects of amphetamine and dopamine agonists in inducing a psychosis with schizophreniform features, it was strengthened by the finding that almost all antipsychotic drugs are effective antagonists of the dopamine D2 receptor subtype. Subsequently, the higher density of dopamine D2 receptors found in post-mortem brain from schizophrenic patients led to the formulation of a modified dopamine hypothesis in which elevated D2 receptors were proposed to underlie the positive symptoms (type I syndrome) of schizophrenia (Crow, 1985). This provided a substantial impetus to neurochemical research in schizophrenia, focusing on the dopamine system. However, problems soon emerged with the interpretation of the increase in D2 receptor density. An up-regulation of D2 receptors is seen in animals after chronic administration of antipsychotic drugs, a treatment that most schizophrenic patients will inevitably have received. It seemed likely, therefore, that the elevation seen was a consequence of drug treatment and unrelated to the disease process. Despite some remaining inconsistencies, most post-mortem and positron emission tomography (PET) studies of D2 receptors conclude that there is no elevation in drug-free schizophrenic patients.

One decade ago it emerged that the D2 receptor subtype was in fact composed of three dopamine receptors with substantial structural and pharmacological similarities, now described as the D2, D3 and D4 receptors. D2 receptors remain the major subtype in striatal and some extrastriatal regions. D3 receptors are mainly expressed in the pallidum and the limbic striatum (nucleus accumbens) and, at the cellular level, may be partly presynaptic. In comparison to D2 receptors they generally have higher affinities for agonists and similar, or lower, affinities for the antipsychotics. Some changes in the D3 receptor and its mRNA have been reported in post mortem tissue in schizophrenia, although it is again hard to exclude the possible effects of prior drug treatment. Nevertheless, D3 is considered by some as a potential target for antipsychotic drugs.

More excitement was generated by the discovery of the D4 receptor. This was found to be expressed, albeit in relatively low amounts, in some regions associated with the pathology of schizophrenia including the amygdala and frontal cortex (Van Tol et al., 1991). The observation that generated the greatest interest in this receptor was the high affinity for D4 shown by the archetypal atypical antipsychotic drug clozapine. There was a potential mechanism, D4 receptor selectivity, that might explain the atypicality and/or increased efficacy of this drug. Furthermore, an initial investigation of the D4 receptor in human brain tissue identified an apparent six-fold increase in the striatum in schizophrenia (Seeman et al., 1993). This finding did much to renew interest in dopamine systems in schizophrenia and to stimulate investment in the search for D4 antagonists as potential antipsychotic drugs. Unfortunately it is now clear that this result was erroneous (Reynolds, 1996). It has not been possible consistently to reproduce the elevation of D4 receptors in schizophrenia, and of the drugs with D4 activity that have reached the clinic, most have proven ineffectual.

3.2 Synaptic dopamine

One of the few studies directly identifying an abnormality in dopamine neurotransmitter in schizophrenia demonstrated a lateralised, left hemisphere, elevation in the amygdala (Reynolds, 1983), which added to the evidence for the view of schizophrenia as a left temporal lobe disorder. This elevation is not, however, interpreted as a primary pathology; it seems likely that it reflects a dysfunction or deficit in the neuronal systems controlling dopaminergic activity, and a correlation with diminished levels of a marker for GABA support this interpretation (Reynolds et al., 1990).

That synaptic dopaminergic activity might be abnormal has received some recent support in the past few years. PET imaging techniques have employed D2 antagonist radioligands that are readily displaceable by dopamine from the brain receptor to provide an indirect indicator of synaptic dopamine levels. This technique relies on the amount of binding of low concentrations of radioligand to the receptor being inversely proportional to the amount of competing synaptic dopamine, thus providing a measure of relative concentrations of dopamine released into the synapse. Using this technique, a relatively greater release of dopamine in the striatum is seen in schizophrenic subjects in comparison to control subjects following amphetamine administration (Laruelle et al., 1996). This dopamine release is proportional to the severity of the psychosis. Breier et al. (1998) have modelled this process by administration of the

psychotogenic glutamate receptor antagonist ketamine, which can also increase release of striatal dopamine, an effect again in proportion to the severity of the induced psychosis, and indicating that abnormal glutamate neurotransmission might underlie the findings in schizophrenia. More recent PET studies involving the depletion of dopamine showed that the usual level of D2 receptor occupancy by dopamine in untreated patients is greater than in control subjects (Abi-Dargham et al., 2000).

There are many factors to consider before accepting that these findings reflect a pathology of the disease. Nicotine can increase dopamine release and schizophrenic patients are frequently heavy smokers. Stress too can increase dopamine release and such stress may be secondary to the symptoms experienced by the patient. Methodological limitations restrict the PET studies of synaptic dopamine to the striatum; it is far from clear whether these changes in dopamine function may also occur in other brain regions that are more strongly implicated in the pathophysiology and pathology of the disease. Nevertheless, one interpretation is that the control of dopamine release is disinhibited in schizophrenia, and that this effect may reflect a decreased glutamatergic function.

Thus there is evidence, albeit circumstantial, of a disturbance of glutamate systems in the disease. In addition there is evidence of GABAergic deficits. Adding to the relevance of these hypotheses of amino acid transmitter dysfunction is the opportunity to relate neurochemical changes directly to a neuronal pathology and, with some further extrapolation, to the aetiology of schizophrenia.

4.   GABAergic deficits

Current understanding of how GABA is implicated in schizophrenia has emerged from the application of modern histological studies that, over the past 15 years, have demonstrated substantial evidence for a neuropathology of the disease. There is evidence that this neuropathology includes GABAergic interneurons. Several studies have determined neuronal density in frontal cortex tissue, some of which indicate no change, or even increased densities in schizophrenia. However, few studies have adequately distinguished pyramidal cells and interneurons. One of the first reports to do this was that of Benes et al. (1991), showing diminished numbers of (presumably GABAergic) interneurons in anterior cingulate and prefrontal cortex. This finding is consistent with a wide range of other studies that, more or less directly, indicate deficits in cor-

tical GABAergic neurons in schizophrenia. As reviewed recently (Reynolds et al., 2001) abnormalities include increases in the GABA-A receptor, and deficits in a variety of proteins present in GABAergic neurons, including the neuropeptides cholecystokinin and somatostatin, the calcium binding protein parvalbumin, the enzyme NADPH diaphorase and the synthetic enzyme glutamic acid decarboxylase (GAD). However, this substantial body of data is not always consistently replicated, and the interpretation of these findings varies between that of a deficit in a subgroup of GABAergic neurons and the suggestion that a diminished expression of protein occurs in otherwise intact neurons. Akbarian et al. (1995) concluded the latter after finding deficits of GAD-immunoreactive cells in the absence of any detectable loss of cortical neurons.

There are some indications that GABAergic axonal innervation is diminished in the cortex in schizophrenia. A deficit of GAD-immunoreactive puncta was reported in frontal cortex (Woo et al., 1998) and hippocampus (Todtenkopf & Benes, 1998), while the cortical plexus of (GABAergic) parvalbumin-immunoreactive fibres is also diminished (Reynolds et al., 2001). The latter two studies reported a positive correlation of these measures of innervation with total antipsychotic drug exposure, indicative of protective or stimulatory effects of chronic drug treatment.

The reduction in nicotinic receptors reported in the hippocampus in schizophrenia is also consistent with a GABAergic neuronal deficit, since these receptors are found on interneurons (Freedman et al., 1995). However, the finding is interpreted as reflecting a more basic role for nicotinic receptor dysfunction in schizophrenia, a hypothesis with support from genetic, neuropsychological and neurophysiological evidence (Adler et al., 1998). Relevant to this is the importance of cholinergic systems in consciousness and the role of cholinergic deficits in the production of hallucinations and cognitive disturbances which are explored elsewhere in this Volume (see Chapters 2, 12 and 13).

5.   Glutamatergic abnormalities

Glutamate systems have long been implicated in the pathophysiology of schizophrenia. Strong if circumstantial evidence comes from the psychosis associated with phencyclidine (PCP) administration; PCP blocks of the ion channel the glutamate/NMDA receptor. Psychosis due to PCP and other noncompetitive NMDA antagonists includes the development of negative as well as positive symptoms and therefore is considered a better model of schizophre-

nia than the primarily positive psychotic syndrome induced by amphetamine (Javitt & Zukin, 1991). The "hypofunction" of NMDA receptors due to PCP has longer-term effects, eventually inducing selective neuronal damage, and this process has led to an important hypothesis relating to a postulated neurodegeneration underlying progressive cognitive dysfunction in schizophrenia (Olney & Farber, 1995). These authors have also shown that neuronal damage due to NMDA receptor hypofunction is mediated by GABAergic neurons. Thus the cortical GABAergic deficit in schizophrenia described above could well be an initial deficit, perhaps of neurodevelopmental origin, that subsequently results in a further, progressive, glutamatergic neuronal loss.

Measures of pyramidal (glutamatergic) neurons have identified either an increase (Selemon et al., 1998) or no significant change (Benes et al., 1986; Pakkenberg, 1993) in cortical tissue in schizophrenia. Similarly, post mortem neurochemical studies do not provide particularly consistent support for glutamatergic dysfunction in the disease, despite many abnormalities being reported (reviewed by Reynolds, 1995). Markers of glutamatergic innervation, glutamate uptake sites defined by radioligand binding, are reportedly decreased in some striatal tissues (Aparicio-Legarza et al., 1997; Simpson et al., 1992) and in temporal cortex (Deakin et al., 1989) in schizophrenia, while the latter study describes an increase in frontal cortex. Glutamate receptors too are changed. For example, early reports indicted the kainate receptor subtype to be elevated in frontal cortex (Deakin et al., 1989) and diminished, albeit not in all studies, in the hippocampus (Kerwin et al., 1990); there is some further support for the latter findings from assessments of receptor subunit mRNA.

More recent studies have looked at the NMDA receptor. Several studies have also determined mRNA for subunits of the NMDA receptor complex. Akbarian et al. (1996) demonstrated a substantial elevation in the NR2D subunit specific to the prefrontal cortex in schizophrenia, interpreted as an indicator of a deficit in glutamatergic transmission via the NMDA receptor site, although there is no report of an increase in receptor density in this region. However in the superior temporal cortex there is an elevation in some radioligand binding to the NMDA receptor (Grimwood et al., 1997), an observation confirmed in a larger series of schizophrenics (Reynolds et al., unpublished results). These findings may be regulatory effects consequent upon a glutamatergic deficit or, alternatively, could reflect some other aetiology resulting in a disturbance of neuronal expression of the receptor. In the basal ganglia at least, this may relate to the extrapyramidal side effects of antipsychotics.

5.1 N-Acetylaspartate deficits

N-Acetylaspartate (NAA) is a metabolic marker of neurons that can be identified in vivo using magnetic resonance spectroscopy (MRS). The function of NAA in the brain is unclear; it is, however, a metabolite of N-acetylaspartyl-glutamate, which has been found to be active at glutamate receptors (Coyle, 1997). An early study found NAA to be reduced in the medial temporal lobe in schizophrenia (Nasrallah et al., 1994), consistent with suggestions of neuronal deficits/dysfunction in the hippocampus/amygdala. Following this report there have been many other investigations identifying NAA deficits in vivo in schizophrenia. Recently, these have included prefrontal cortical losses that correlate with the increase in dopamine release in the striatum (Bertolino et al., 1999), an intriguing finding in the light of the interpretation that striatal dopamine dysfunction in schizophrenia might reflect deficits of corticostriatal glutamatergic innervation. There are also reports a relationship of cortical NAA losses with deficit schizophrenia (Delamillieure et al., 1999) and a correlation with disease duration, indicative of a degenerative process (Ende et al., 2000). These findings are consistent with a hypothesis relating deficits of NAA, as a marker for neuronal integrity, to the neurodegeneration underlying cognitive decline, providing some support for the process, if not the initial mechanism, of the NMDA hypofunction hypothesis discussed above.

6.   Clinical correlates of neurotransmitter abnormalities

The deficit of cortico-striatal innervation that is presumably responsible for reported losses of striatal glutamate uptake sites (Aparicio-Legarza et al., 1997; Simpson et al., 1992), is likely to contribute to the cognitive dysfunction of schizophrenia. These have been described as having similarities to the subcortical dementia (Pantelis et al., 1992) seen in a variety of neurodegenerative disorders; disturbances of corticostriatal function are thought to underlie this pattern of cognitive deficits that include disturbances of attention, executive function and short-term memory.

The pre- and post-synaptic indicators of glutamatergic changes in the cortex suggest differential effects between temporal and frontal cortex, although consensus amongst the various reports is lacking. These changes in glutamatergic markers can be interpreted as losses of neuropil with a consequent increase in the density of glutamatergic synaptic markers or, at the other extreme, as deficits in innervation, which may result in a compensatory upregulation of

receptors. Neuroimaging data suggest that functional frontal cortical deficits may relate to negative symptoms, while certain changes in temporal cortical function correlate with e.g. auditory hallucinations. Such neurochemical-behavioural correlates cannot be undertaken in isolation; interaction of the GABAergic deficits and other neurotransmitter abnormalities with glutamatergic abnormalities is likely to occur. In addition, imaging data such as that from fMRI or blood flow measures may correlate with behaviour but not necessarily indicate the neuronal origins of the functional disorder underlying symptom expression.

One essential consideration is the aetiology of these neurotransmitter abnormalities; the evidence is at best circumstantial. However, identification of deficits in neurons immunopositive for the CBP parvalbumin, a marker for a subtype of GABergic neurons, provided the basis for a hypothesis for the developmental origins of GABAergic losses. Of the three CBP's in the human frontal cortex, parvalbumin is expressed relatively late (i.e. at 3–6 months postnatally), indicating that there may be a period of vulnerability of this subtype of GABAergic neurons prior to the expression of the presumably protective CBP. Factors such as viral infection in utero and obstetric complications have been implicated in schizophrenia, and these aetiologies have been hypothesised to lead to subtle neurotoxic effects that may preferentially affect such vulnerable neurons (Beasley & Reynolds, 1997). The hypothesis discussed above, that glutamate/NMDA receptor hypofunction may result in a late-onset neuronal damage underlying cognitive changes in schizophrenia, provides a mechanism for the pathogenesis of glutamatergic systems occurring later in life and as a consequence of GABAergic neurons deficits (Olney & Farber, 1995).

While these proposals provide useful and testable hypotheses, they are based on slim evidence from post mortem neurochemistry of schizophrenia. Since the deficits in GABAergic markers may be interpreted as demonstrating neuronal hypofunction rather than cell loss, they could equally be ascribed to a consequence of, rather than a cause of, glutamatergic abnormalities. It would be valuable to identify temporal changes in neurochemistry over the disease course, rather than end-stage information that most post-mortem studies inevitably provide, as well as more information from individuals at risk for schizophrenia.

Neurochemical imaging and MRS techniques have obvious, although long-term studies of neurochemistry in vivo have yet to be applied to schizophrenia. One correlate of the neurodegenerative process proposed in the NMDA receptor hypofunction hypothesis is demonstrated in the relationship between anterior cingulate NAA deficits and disease duration (Ende et al., 2000). A

further indication of a neurochemical-aetiological correlate is that of NAA deficits in the hippocampus, that are present in unaffected siblings as well as schizophrenic subjects (Callicott et al., 1998), suggestive of a genetic indicator. However, studies of the neurochemical and other pathological correlates of aetiology are limited by both the complexity and lack of knowledge of aetiological factors in schizophrenia. Nevertheless, the identification of syndromes within the disease which correlate with functional brain abnormalities has contributed to indicating the relationship between neurotransmitter pathologies and symptom profiles, leading eventually to an understanding of the relationship between neurochemistry and behaviour, including that associated with disturbances of conscious awareness, in schizophrenia (see Table 1). Amongst these relationships, dopaminergic overactivity correlating with psychotic symptoms probably provides the most fertile ground for linking a specific neurotransmitter to alterations in consciousness in schizophrenia.

7. Summary

For half a century, neurochemical investigations have played a major part in efforts aimed at understanding the brain dysfunction underlying schizophrenia. From the search for endogenous hallucinogens, as proposed by the transmethylation hypothesis, via a multiplicity of theories implicating abnormality of function or metabolism of various neurotransmitters, these neurochemical approaches have provided a focus for biological research into the disease as well as a stimulus to antipsychotic drug development. These approaches have often been naïve, over-developed elaborations based on minimal, or incorrect, data. Although not totally immune from these caveats, the dopamine hypothesis has nevertheless provided a valuable stimulus to neuroscientific research into schizophrenia over the past three decades. It is also likely to be the most relevant to disturbances in consciousness in schizophrenia.

Recent evidence for the view of schizophrenia as a biological disorder has come from neuropathological research. Reflecting advances in both *in vivo* imaging techniques and quantitative histology, schizophrenia is now interpreted as a disease with unequivocal, if subtle, deficits in structure and function of certain brain regions. These deficits are considered, at least in part, to have their origins in early brain development; schizophrenia is now considered a neurodevelopmental disorder, a concept not necessarily at odds with its (partial) genetic origins.

Table 1. Some neurotransmitter and synaptic abnormalities in schizophrenia, their possible underlying pathologies and hypothetical symptom correlates

Region	Neurochemical pathology	Possibly due to:	Symptom correlate or consequence
Striatum	↑Dopamine D2 receptors	Drug treatment with D2 antagonists	Components of EPS?
Striatum	↑Dopamine release	↓cortico-striatal innervation?	Psychosis, psychomotor dysfunction
Striatum	↓Glutamate uptake sites	↓cortico-striatal innervation	Cognitive dysfunction
Amygdala	↑Dopamine (lateralised)	↓inhibition of dopamine reflecting neuronal deficits in temporal lobe	Positive symptoms (reality distortion)?
Hippocampus and cortex	↓ 5-HT2A receptors	Selective ↓in density or function of GABAergic neurons; drug treatment?	?
Hippocampus	↓CCK, somatostatin, GAD, calcium binding proteins, nicotinic receptors	Selective ↓in density or function of subtypes of GABAergic neurons	Positive symptoms (reality distortion)— in left hemisphere
Cortex	↓CCK, somatostatin, GAD, calcium binding proteins	Selective ↓in density or function of subtypes of GABAergic neurons	Negative and/or cognitive symptoms
Frontal cortex	↓glutamate receptors, ↑glutamate uptake sites ↑ 5-HT1A receptors	↑density of glutamatergic innervation	Negative and/or cognitive symptoms
Temporal cortex	↑glutamate receptors	↓density of glutamatergic neurons	reality distortion, cognitive deficits

This table provides a speculative attempt at integrating neurotransmitter-related abnormalities reported in schizophrenia with their presumed origins and possible symptom correlates. There are some apparent inconsistencies, notably in some striatal abnormalities that may share a pathogenic mechanism but have been proposed to relate to different behavioural consequences. Although not comprehensive, and influenced the author's studies and viewpoint, it illustrates the relationship of biological dysfunction at the cellular level to that integrative behaving. An appreciation of this relationship is essential for the eventual understanding symptom aetiology of pharmacotherapeutic mechanisms of symptom relief.

These regional pathologies of the brain have provided some understanding of the functional neurobiology of the symptoms of the disease. They have not yet contributed to providing a rational basis on which to understand antipsychotic mechanisms. Neurotransmitter correlates of neuropathology can, in theory at least, identify the aberrant systems that are normalised by antipsychotic drug action. Modern imaging techniques have also contributed to *in vivo* neurochemical studies that supplement post mortem investigations. In addition to dopamine, neurotransmitter systems currently receiving particular research interest are GABA and glutamate. Despite some contradictory reports, evidence now strongly implicates a cortical pathology in schizophrenia of subtypes of GABAergic neurons, while glutamatergic synapses are sites of other reported abnormalities. It will be interesting to determine whether GABA or glutamate abnormalities relate specifically to the clinical symptoms in schizophrenia, including those affecting consciousness.

References

Abi-Dargham, A. et al. (2000). *Proceedings of the National Academy of Science USA* 97, 8104–8109.

Adler, L.E. et al. (1998). *Schizophrenia Bulletin* 24, 189–202.

Akbarian, S. et al. (1995). *Archives of General Psychiatry* 52, 258–266.

Akbarian, S. et al. (1996). *Journal of Neuroscience* 16, 19–30.

Aparicio-Legarza, M.I. et al. (1997). *Neuroscience Letters* 232, 13–16.

Beasley, C.L. & G.P. Reynolds (1997). *Schizophrenia Research* 24, 349–355.

Benes, F.M. et al. *Biol.* (1986). *Archives of General Psychiatry* 43, 31–35.

Benes, F.M. et al. (1991). *Archives of General Psychiatry* 48, 996–1001.

Bertolino, A. et al. (1999). *Biological Psychiatry* 45, 660–667.

Breier, A. et al. (1998). *Synapse* 29, 142–147.

Callicott, J.H. et al. (1998). *Psychiatry* 44, 941–950.

Coyle, J.T. (1997). *Neurobiological Disorders* 4, 231–238.

Crow, T.J. (1985). *Schizophrenia Bulletin* 11, 471–486.

Deakin, J.F.W. et al. (1989). *Journal of Neurochemistry* 52, 1781–1786.

Delamillieure, P. et al. (2000). *American Journal of Psychiatry* 157, 641–643.

Ende, G. et al. (2000). *Schizophrenia Research* 41, 389–395.

Freedman, R. et al. (1995). *Biological Psychiatry* 38, 22–33.

Frith, C.D. (1992). *The Cognitive Neuropsychology of Schizophrenia.* Hove: Erlbaum.

Grimwood, S. et al. (1999). *Neuroreport* 10, 461–465.

Javitt, D.C. & S.R. Zukin (1991). *American Journal of Psychiatry* 148, 1301–1308.

Joyce, J.N. et al. (1993). *Neuropsychopharmacology* 8, 315–336.

Kerwin, R.W. et al. (1990). *Neuroscience* 39, 25–32.

Laruelle, M. et al. (1996). *Proceedings of the National Academy of Science USA* 93, 9235–9240.

Liddle, P.F. et al. (1992). *British Journal of Psychiatry* 160, 179–186.

Nasrallah, H.A. et al. (1994). *British Journal of Psychiatry* 165, 481–485.

Olney, J.W. & N.B. Farber (1995). *Archives of General Psychiatry* 52, 1015–1018.

Owen, F. & M.D.C. Simpson (1995). In S.R. Hirsch & D.R. Weinberger (Eds.), *Schizophrenia* (358–378). Oxford: Blackwell.

Pakkenberg, B. (1993). *Psychiatry* 34, 768–372.

Pantelis, C. et al. (1992). *British Journal of Psychiatry* 160, 442–460.

Reynolds, G.P. (1983). *Nature* 305, 527–529.

Reynolds, G.P. (1995). *International Review of Neurobiology* 38, 305–339.

Reynolds, G.P. (1996). *Drugs* 51, 7–11.

Reynolds, G.P. et al. (2001). *Brain Research Bulletin* (in press).

Reynolds, G.P. et al. (1990). *Biological Psychiatry* 27, 1038–1044.

Seeman, P. et al. (1993). *Nature* 365, 441–445.

Selemon, L.D. et al. (1998). *Journal of Comparative Neurology* 392, 402–412.

Simpson, M.D. et al. (1992). *Psychiatry Research* 42, 273–282.

Todtenkopf, M.S. & F.W. Benes (1998). *Synapse* 29, 323–332.

Van Tol, H.H.M. et al. (1991). *Nature* 350, 610–614.

Woo, T.U. et al. (1998). *Proceedings of the National Academy of Science USA* 95, 5341–5346.

Mood disorders

R. Hamish McAllister-Williams

1. Introduction

Mood (affective) disorders include depressive illness and bipolar affective disorder (manic depression). They are extremely common with a point prevalence of 5–10% in the general population. They range from severe disorders accompanied by psychotic symptoms to milder disorders that merge into normality, and are characterised by constellations of symptoms, at the heart of which are changes in mood, interest and enjoyment of normal activities. In addition to these core symptoms, 'biological' symptoms occur, such as changes in sleep patterns and activity levels, as do psychological symptoms, such as alterations in beliefs of self worth and abnormalities of neuropsychological function including episodic and working memory.

Consciousness can be argued to include a subjective component, that may be viewed as "representational awareness" (Donald, 1995) located in a spatio-temporal context (Delacour, 1995) and objective components, that have been referred to as an "architectural" concept of consciousness (Donald, 1995). The latter includes the ability to detect and adapt to novelty, to integrate and control behavior particularly towards a goal, to use language, to generate imagery and to initiate recall from declarative (episodic) memory. Consciousness can be viewed as an epiphenomenon of these abilities, however many argue on the basis of neuropsychological studies for a central processor (Donald, 1995), a supervisory system (Shallice, 1988) or "executive control." Such ideas are particularly evident in theories of working or short term memory (Shah & Miyake, 1999), and indeed some have equated working memory to the content of consciousness (Atkinson & Shiffrin, 1971).

Mood disorders produce impairments in many domains relevant to a debate on the biology of both the subjective and objective components of consciousness. Thus a description of the neurochemistry believed to be important

in depression may be of relevance to consciousness. This chapter will examine some of the symptoms seen in affective disorders that indicate an impairment in consciousness occurs in these illnesses. It will then examine some selected hypotheses regarding the neurochemical underpinnings of mood disorders suggesting that these are also relevant to the neurochemistry of consciousness.

2. Depressive symptoms and consciousness

Representational awareness requires the spatio-temporal representation of mental images. All such abstract thought has some affective tone and emotional background (Delacour, 1995). Since the core symptom of affective disorders is a change in affect, such disorders must involve a change in consciousness in some way. Indeed at the turn of the century many theoretical models of consciousness centered on affective and emotional disturbances (Markowitsch, 1995). This is not difficult to understand given the profound alterations in a person's view of himself and the world around him when suffering from an affective disorder. This view is sometimes reported by depressed patients, for example, as sounds being heard as 'dull', colors being 'drab', and food 'lacking taste'. By contrast, anxious and agitated patients can report being hypersensitive to sensory perceptions.

2.1 Psychotic symptoms

In the most severe cases, affective disorders are associated with profound changes in perception and thought content with the occurrence of psychotic symptoms. These most typically take the form of hallucinations (perceptions in the absence of a stimuli) and delusions (fixed, firmly held beliefs despite a lack of evidence and out of social, religious or cultural context for that person). In affective disorders, as opposed to schizophrenia, such symptoms tend to be mood congruent—that is the content of the hallucinations or delusions are congruent upon the prevailing mood of the individual. Such symptoms represent an alteration in the representational awareness of the individual and have been argued to be "aberrations of conscious experience" such that models of psychotic symptoms must necessarily incorporate models of consciousness itself (Gray, 1995). Indeed, the occurrence of hallucinations demonstrates a fundamental abnormality in the individual's ability to generate imagery, a proposed component of consciousness (Donald, 1995). The nature of the hallucinations in mood disorders tend to be less complex than those seen in

schizophrenia and there is usually an absence of a breakdown of ego boundaries that help the individual differentiate themselves from the world around them. However, the nihilistic and grandiose nature of delusions seen in mood disorders leads to impairments in many other elements of the objective architecture of consciousness, in particular the ability to detect and adapt to novel situations.

2.2 Behaviour

Both depression and mania can impair goal directed behaviour even in the absence of psychotic symptoms. Depressed patients frequently lack motivation and the necessary energy to obtain a goal. Manic patients' behavior is often so chaotic as to preclude completion of particular projects despite the patients' (exaggerated) belief in their own abilities. The spatio-temporal context of individuals suffering from affective disorders can also be impaired. Depressed patients often perceive the day as 'dragging on', while the manic typically feels that time is speeded up and there are not enough 'hours in the day' to complete all the tasks they have set themselves. These subjective symptoms are mirrored by more objective evidence of retardation or acceleration of thought and movement, most clearly demonstrated by slowed speech with poverty of content or over-inclusive pressured speech. The use of language is an important facet of consciousness since this allows representation of facets of ourselves, and our interactions with the world at large, that could not occur simply via mental imagery (Delacour, 1995).

2.3 Sleep

Sleep disturbances are an integral feature of mood disorders, with over 90% of depressive patients experiencing some problems (Thase, 1998). Like the disorders themselves, the sleep disturbances associated with depression are heterogeneous, ranging from hypersomnia to marked difficulties maintaining sleep. However, the disturbance seen in mania is usually a reduction in quantity. Polysomnographic recordings can be used to document sleep maintenance difficulties and these often reveal reduced slow wave sleep, early onset of the first episode of rapid eye movement (REM) sleep, and increased phasic REM sleep in depression (Perlis et al., 1997). While some of these abnormalities are state dependent, reverting to normal on clinical recovery, others may be trait markers or at least predictive indicators of depressive relapse (Thase et al., 1998). The changes in sleep pattern may reflect a heightened arousal during sleep in

depressed individuals (Perlis et al., 1997). REM or paradoxical sleep and wakefulness have been argued to be fundamentally identical states with the provision that the handling of sensory information is altered in REM sleep (Pare & Llinas, 1995). If this is the case, then the dramatic alterations in REM sleep seen in depression may index an alteration in consciousness.

2.4 Episodic memory

The retrieval of memory for a specific event, episodic memory, can be viewed as a fundamental component of consciousness (Donald, 1995). Numerous studies demonstrate an impairment of episodic memory in mood disorders. It has been suggested that the impairment is caused by poor motivation and an inability to sustain effort on memory tasks (Cohen et al., 1982). However, detailed neuropsychological testing indicates that reduced effort is not the major determinant of impaired performance (Austin et al., 1992). While early studies suggested a correlation between memory impairment and the degree of mood disturbance (Cohen et al., 1982), this has been challenged by more recent studies (Ilsley et al., 1995; Young et al., 2000). In addition, neuropsychological impairments persist in clinically recovered depressives (Ferrier et al., 1991; Bahrainian et al., 1995) and in euthymic bipolar affective disorder patients (Ferrier et al., 1999). These findings support the notion that impaired memory is not simply an epiphenomenon of depressed mood and that psychological factors alone are unlikely to account for the impairments. However it has been argued that memory impairments are most evident in older but not younger (less than 50 years old) depressives (Elliott, 1998). Nevertheless, the impairment in episodic memory seen in at least some groups of affective disorder patients suggests that these illnesses involve an impairment of consciousness. Since the impaired memory persists in patients when neither depressed nor manic, the pathophysiology underlying this abnormality must relate to trait vulnerability rather than mood state.

2.5 Information processing

In line with perceptual distortions and mood congruent hallucinations, patients with affective disorders frequently demonstrate mood congruent biases in information processing. Depressed patients are oversensitive to negative feedback and perceived failure during memory recall tests, being more likely than matched controls to make an error following a previously identified error (Elliott et al., 1996). However, the most reliably reported bias is in memory

studies in which depressed patients show a facilitation of recall of unpleasant compared to pleasant material (Blaney, 1986), especially for autobiographical episodic memory (Williams & Scott, 1988).

2.6 Executive function

One of the most compelling pieces of evidence supporting the notion that a disturbance of consciousness occurs in affective disorders is the finding of impaired working memory and executive function in patients. While some reviewers suggest that the neuropsychological impairment in depression is global (Christensen et al., 1997), others have argued that, compared to episodic memory, executive function is particularly impaired (Veiel, 1997), especially in younger depressed patients (Elliott, 1998). As previously discussed, working memory has been equated with the content of consciousness by some (Atkinson & Shiffrin, 1971). Further, while many disparate psychological models of working memory exist, many of these posit a central role for an executive component (Shah & Miyake, 1999), with many authorities defining this as the functional equivalence of consciousness itself (Shallice, 1988; Donald, 1995). An impairment of executive function then may be the most direct and objective sign that consciousness is impaired in affective disorders.

3.   Neurochemical abnormalities in affective disorders

Original theories concerning the neurochemistry of affective disorders centered around hypotheses of low concentrations of monoamines. Such theories have been rejected due to a lack of consistent evidence of low concentrations of monoamines or their metabolites in plasma, CSF or brains of patients, though most authorities continue to argue for an involvement of monoaminergic systems in the pathophysiology and treatment of affective disorders. Monoamine system abnormalities indeed are consistent with notions of alterations in consciousness in affective disorders if the locus ceruleus, and the raphé nuclei are part of the anatomical substrate of consciousness (Delacour, 1995). However, these original theories are inherently flawed since they posit that not only are affective disorders homogeneous but that all the symptoms found in the disorders must be caused by a single neurochemical abnormality. More recently the relationship between various symptoms and specific impairments in neurotransmitter systems have been examined. For example, evidence for a role of dopamine in the pathophysiology of depression comes from a number of

sources. Parkinson's disease, which is characterised by a deficit of dopaminergic neurones, is associated with high rates of depression (Chapter 15). In addition the role of the dopaminergic system in psychotic symptoms has been reviewed by Gray (1995) and in psychomotor retardation by Austin and Mitchell (1995). Dopamine systems are also important in central reward and punishment systems (Chapter 5), and the characteristic pervasive anhedonia seen in depressive illnesses, suggests an abnormality in this system in depression. It is unlikely that a single neurochemical abnormality can explain the diversity of symptoms seen in mood disorders. Indeed some symptoms may reflect multiple pathology. A deficit of serotonergic neurotransmission, a relative increase in pontine cholinergic activity, and an excess of noradrenergic and corticotropin-releasing hormone activity, for example, have been implicated in the pathogenesis of the sleep disturbances of more severe depressive disorders (Thase, 1998).

3.1 Serotonin, the hypothalamic-pituitary-adrenal axis and neuropsychological impairment

Neuropsychological impairments in mood disorders, particularly those of working memory and executive function, are the most convincing and objective demonstrations of an impairment of consciousness. Since these impairments do not correlate with the severity of the mood disturbance and persist upon recovery they are not simply epiphenomena of the mood disturbance but rather may index trait pathology in susceptible individuals. It has previously been argued that mood disturbance and neuropsychological impairment may result from disturbances in two different neurochemical systems, the serotonin (5-HT) system and the hypothalamic-pituitary-adrenal (HPA) axis, between which there is a close interaction (McAllister-Williams et al., 1998).

3.2 The serotonergic system and depression

Drugs that selectively enhance the serotonergic system (selective serotonin re-uptake inhibitors (SSRIs) such as fluoxetine) are highly effective in treating depression. In addition, studies of the effect of lowering central 5-HT levels by dietary manipulation of the 5-HT precursor tryptophan also support a role for 5-HT in the pathophysiology of depression. Initial investigations using this technique found that rapidly lowering brain tryptophan levels (and hence 5-HT) led to a small but significant lowering of mood in healthy subjects (Young et al., 1985). However this finding has not been replicated by other groups (Abbott et al., 1992). It is now believed that a lowering of mood in response to

tryptophan depletion is only apparent in subjects with a vulnerability to depression, such as patients with a strong family history of depression (Benkelfat et al., 1994) and euthymic subjects on no treatment but with a history of recurrent depression (Smith et al., 1997). Rapid tryptophan depletion also leads to a relapse in recovered depressives on medication (Delgado et al., 1990), although this may only occur in patients treated with antidepressants active on the 5-HT system (Salomon et al., 1993). The striking finding in this situation is a temporary return of identical symptomatology that the patient experienced during the episode of illness. For example patients who had feelings of inappropriate guilt when ill experience a return of these same feelings with an identical content. This finding supports the notion that the affective biasing of perception and information processing may have a serotonergic basis.

While the response to acute tryptophan depletion suggests a role for the 5-HT system in general in mood disorders, the precise consequences of rapid lowering 5-HT on the functional activity of the serotonergic system remains unknown. Deakin and Graeff (1991) suggested that activation of 5-HT neurones in the raphé that project onto postsynaptic $5\text{-}HT_{1A}$ receptors in hippocampus maintains adaptive behaviors in the face of aversive stimuli. They further hypothesise that a failure of this system leads to helplessness in animals and depression in humans. This model predicts that the mood lowering effect of tryptophan depletion in humans is a result of reduced transmission through postsynaptic $5\text{-}HT_{1A}$ receptors in hippocampus (Deakin & Graeff, 1991). Endocrine responses to L-tryptophan are believed to be an indicator of postsynaptic $5\text{-}HT_{1A}$ function (Smith et al., 1991) and five studies have reported a blunted growth hormone (GH) or prolactin response to L-tryptophan in depressed patients compared to controls (see Power & Cowen, 1992). An impairment in postsynaptic $5\text{-}HT_{1A}$ receptors in depression has also been suggested by recent imaging studies which have revealed a small but significant reduction in receptor numbers in depressed patients compared to controls (Sargent et al., 2000; Drevets et al., 2000).

Further support for Deakin and Graeff's model (1991) comes from studies of the mechanism of action of antidepressants. *In vivo* studies in rodents have demonstrated that a range of antidepressants and electroconvulsive shocks, when given chronically but not acutely, attenuate the function of autoinhibitory $5\text{-}HT_{1A}$ receptors on serotonergic neurones in the raphé nuceli (Goodwin et al., 1985). Attenuation of these autoreceptors enhances serotonergic transmission generally, including to the hippocampus. Chronic treatment of depressed patients with a variety of antidepressants, including TCAs (Cowen et al., 1990), MAOIs (Price et al., 1985) and SSRIs (Price et al., 1989), enhances

the prolactin response to L-tryptophan, again suggesting increased neurotransmission at postsynaptic 5-HT_{1A} receptors.

3.3   The serotonergic system and neuropsychological impairment

In contrast, the role of the 5-HT system in neuropsychological function is unclear. In rats, inhibition of 5-HT synthesis improves learning (Brody, 1978), but in mice the opposite effect is seen (Valzelli & Pawlowski, 1979). McEntee and Crook (1991) argue that stimulation of 5-HT activity impairs learning and memory, while impairment of 5-HT neurotransmission enhances it. However many of the studies reviewed by McEntee and Crook used non-selective 5-HT ligands and 5-HT may have varying effects at different receptor subtypes. The selective 5-HT_{1A} receptor agonist flesinoxan can dose dependently impair working memory in rats, an effect believed to be mediated at hippocampal postsynaptic 5-HT_{1A} receptors (Carli et al., 1995). These are the same receptors as postulated to be involved in mood disturbances (Deakin & Graeff, 1991) though an impairment in transmission at this site, as seen with a 5-HT_{1A} antagonist, improves memory in animals (Harder et al., 1996) as opposed to the impairment seen in depression.

Tryptophan depletion in healthy volunteers impairs the retrieval of learnt material (Park et al., 1994), an effect probably mediated through a selective impairment of episodic memory consolidation (Riedel et al., 1999; Schmitt et al., 2000). However, tryptophan depletion appears to have no effect on working memory (Riedel et al., 1999) and either no effect or an enhancement of tests of executive function (Park et al., 1994; Schmitt et al., 2000). Thus the abnormality in episodic memory in mood disorders could conceivably be related to an impairment in the 5-HT system, but such an impairment is unlikely to account for the abnormalities in working memory and executive function. Clearly then, changes in consciousness occurring in affective disorders are unlikely to be explainable on the basis of an abnormality in a single neurochemical system.

3.4   The HPA axis and depression

The HPA axis has been hypothesised to be of aetiological importance in depressive illnesses (McAllister-Williams & Young, 1998; McAllister-Williams et al., 1998). Severely depressed patients (Sachar et al., 1973) and bipolar disorder patients (Linkowski et al., 1985) have significantly raised cortisol concentrations compared to controls. Imaging studies show an enlargement of the adrenal cortex in depressed patients compared to healthy subjects (Nemeroff

et al., 1992; Rubin et al., 1996). This hyperplasia correlates with cortisol levels in depression (Nemeroff et al., 1992), and, along with normalisation of cortisol levels, appears to disappear following recovery (Rubin et al., 1996).

Abnormality in the regulatory feedback mechanism may explain the over-activity of the HPA axis seen in depressed patients, since a lack of dexamethasone suppression of cortisol secretion is observed (Carroll et al., 1981). In addition, despite a hypercortisolaemia, depressive patients generally do not demonstrate Cushingoid features, possibly because of a reduction in the function of corticosteroid receptors. It has therefore been hypothesised that the primary abnormality in depression may thus be an impairment of corticosteroid receptor function (Barden et al., 1995).

The findings of raised corticotropin releasing hormone (CRH) levels in CSF (Banki et al., 1992) have led to hypotheses of abnormalities in hypothalamus being central to depression (Nemeroff, 1996). Animal studies have demonstrated that CRH administration can lead to decreased appetite, disrupted sleep and psychomotor alterations (Heinrichs et al., 1995) leading to the proposal that excess CRH acts on extra-pituitary sites to produce some of the symptoms of depression (Nemeroff, 1996). However, other than findings of high rates of depression in Cushing's syndrome patients (Kelly et al., 1983), there is little evidence, (or hypothesised mechanisms) that raised levels of corticosteroids mediate a lowering of mood in depression. Indeed, acute administration of cortisol to depressed patients causes a transient elevation in mood (Goodwin et al., 1992), and so the relationship between HPA axis abnormalities and low mood in depression is unclear.

3.5 The HPA axis and neuropsychological impairment

There is, however, evidence of a relationship between HPA axis abnormalities and neuropsychological impairments in mood disorders. High levels of endogenous corticosteroids in Cushing's disease are associated with significant impairments of memory that correlate with the plasma level of cortisol and ACTH (Starkman et al., 1986). Healthy volunteers given corticosteroids also show neuropsychological impairments on a range of neuropsychological tests (Wolkowitz et al., 1990; Young et al., 1999; de Quervain et al., 2000). These studies have demonstrated impairments in episodic memory resulting from disruptions of the retrieval of information (de Quervain et al., 2000) and errors of commission in tests of learning which parallel the findings in depressed patients (Wolkowitz et al., 1990). In addition to impaired episodic memory,

working memory and executive function also appear to be impaired by cortisol administration (Young et al., 1999).

Rubinow et al. (1984) have reported a positive correlation between neuropsychological impairment and urinary cortisol and several groups have found greater neuropsychological impairment in depressives who do not suppress cortisol in response to dexamethasone, compared to those who do (Brown & Qualls, 1981; Winokur et al., 1987; Wolkowitz et al., 1990), although this is disputed (Caine et al., 1984). Wauthy et al. (1991) have also found a significant positive correlation between neuropsychological impairment and plasma cortisol concentrations and have suggested that some of the previous discrepancies may be the result of different methods of assessing HPA function (Wauthy et al., 1991). Some support for this notion comes from a recently conducted large study in drug-free depressed patients. While these patients had impairments in working memory and executive function, no difference in cortisol concentrations were apparent compared to healthy controls (Young et al., 2000). However, these neuropsychologically impaired depressed patients were found to have an elevation of their cortisol/dehydroepiandrosterone (DHEA) ratio compared to controls (Young et al., unpublished observation). This finding is of interest since it is believed that DHEA may counteract the deleterious effects of corticosteroids on neuropsychological function (Kaminska et al., 2000).

In summary, the neuropsychological impairment seen in depression may result from the concomitant hypercortisolaemia. This is in contrast to evidence suggesting that serotonergic dysfunction may lead to impairments in episodic memory, but not in working memory and executive function. Therefore the presence of both a mood disturbance, for which there is strong evidence for a serotonergic abnormality, and working memory and executive function impairments in depression suggests a role for both the 5-HT system and the HPA axis in the pathophysiology of the illness and the alterations in consciousness seen. This may appear to be a less than parsimonious hypothesis. However there is a large degree of interaction between the 5-HT system and the HPA axis.

3.6 Serotonergic-HPA axis interactions

These interactions have been extensively reviewed (e.g. McAllister-Williams & Young, 1998). Central to these interactions are 5-HT$_{1A}$ receptors. The discussion below will concentrate on these receptors.

Serotonergic effects on HPA axis function. Serotonergic mechanisms exert an excitatory influence on the entire HPA axis. For example, local application of 5-HT into the hypothalamus produces a dose-dependent increase in CRH release with 5-HT_{1A} receptors possibly being involved (Calogero et al., 1989) and 5-HT directly elicits ACTH release from the pituitary by activation of 5-HT_{1A} receptors (Calogero et al., 1990). 5-HT also has effects on corticosteroid receptors. Neurotoxic lesions of serotonergic neurones in rats causes a reduction of corticosteroid receptor mRNA expression in hippocampus (Seckl & Fink, 1991), while the application of 5-HT increases corticosteroid receptor sites, an effect mediated by 5-HT_{1A} receptors (Budziszewska et al., 1995). Thus the 5-HT system acting through 5-HT_{1A} receptors may be able to modulate the negative feedback control of the HPA axis.

Corticosteroid effects on serotonergic function. Corticosteroids play a modulatory role on central serotonergic function. There is a complex relationship between the amplitude of the corticosteroid stimulus (or the dose of exogenously administered corticosteroid) and the response of the 5-HT system. In many circumstances this response is 'bell-shaped' illustrating a key role of corticosteroids in maintaining homeostasis and results from the activation of two populations of corticosteroid receptors, mineralocorticoid (MR) and glucocorticoid (GR). MRs are found in the limbic system (including the hippocampus), whilst GRs are widely distributed, but enriched in the hippocampus, hypothalamus and in the cell bodies of monoaminergic (including serotonergic) neurones (Aronsson et al., 1988). MRs display a 10-fold higher affinity for corticosterone relative to GRs, resulting in high MR occupancy, even in conditions of low circulating levels of corticosterone. GRs, conversely, are only extensively occupied at times of high corticosterone levels, such as at the time of peak circadian levels and during stress.

Many groups have observed increases of 5-HT_{1A} receptor binding in hippocampus following adrenalectomy that are reversed by administration of corticosterone (Chalmers et al., 1994; Nishi & Azmitia, 1996; Le Corre et al., 1997). This effect of corticosterone is mediated via GRs (Chalmers et al., 1994) influencing 5-HT_{1A} receptor transcription (Nishi & Azmitia, 1996). In rats, repeated stress has been found to decrease hippocampal 5-HT_{1A} receptor numbers (Watanabe et al., 1993). Hippocampal single cell electrophysiological studies have demonstrated that MR activation decreases postsynaptic 5-HT_{1A} mediated hyperpolarisation (Joels et al., 1991), while selective GR agonists block this MR effect, though GR agonists alone have no effect (Joels & de Kloet, 1992). Thus the effects of corticosteroids on postsynaptic 5-HT systems vary with circadian variation in plasma levels and the relative balance between MR

and GR activation. In man, hydrocortisone has been shown to attenuate buspirone induced cortisol release and hypothermia in man (Young et al., 1994) and the GH response to L-tryptophan (Porter et al., 1998), suggesting that corticosteroids have similar effects on postsynaptic 5-HT$_{1A}$ receptors in man as in rodents.

In the dorsal raphé nucleus GR agonists cause a reduction in the functional activity of 5-HT$_{1A}$ autoreceptor mediated inhibition of cell firing (Laaris et al., 1995), an effect likely to be on receptor-effector coupling since there is no change in the number of 5-HT$_{1A}$ receptors (Laaris et al., 1995). *In vivo* models of somatodendritic 5-HT$_{1A}$ function, such as hypothermia in mice, are attenuated by corticosterone administration (McAllister-Williams et al., 2001), in agreement with this electrophysiological data.

It therefore appears that inhibitory somatodendritic 5-HT$_{1A}$ receptor function is reduced by GR activation, leading to an enhancement of 5-HT neurotransmission generally, while the effects of corticosteroids on postsynaptic receptor function depends on the level of circulating corticosteroid differentially activating MR or GR receptors.

4.   Conclusions

The nature of the neurochemical impairment underlying depressive illness remains elusive. There is a great deal of evidence supporting roles for the 5-HT system and the HPA axis. However the evidence is less clear that an abnormality in one system alone can explain the full extent of the clinical features of depressive illness. Subtle abnormalities in the interactions between the HPA axis and the serotonergic system may lead to profound alterations in the functioning of both systems, and it may be this that results in the range of symptoms found in mood disorders.

One hypothesis is that an impairment of serotonergic transmission through hippocampal 5-HT$_{1A}$ receptors may underlie the low mood seen in depression. In addition, the reduced activation of hippocampal 5-HT$_{1A}$ receptors may decrease the inhibitory control of the HPA axis mediated by the hippocampus leading to hypercortisolaemia and a neuropsychological impairment. An alternative hypothesis is that the primary neurobiological disturbance in depression is an abnormality of GRs leading to an impaired feedback control of the HPA axis and hypercortisolaemia. This in turn may lead to neuropsychological dysfunction. Reduced functional activity of GRs may increase the autoinhibitory action of somatodendritic 5-HT$_{1A}$ receptors, decrease 5-HT$_{1A}$ receptor num-

bers in hippocampus, and allow an increased MR attenuation of hippocampal 5-HT$_{1A}$ receptor activation. Thus the net serotonergic transmission through 5-HT$_{1A}$ receptors in hippocampus would be reduced (by several mechanisms) with a probable lowering of mood.

These interactions between the 5-HT system and the HPA axis may be not only be fundamental to the pathophysiology of affective disorders but may also relate to consciousness. If serotonergic abnormalities relate to affective changes, these may be responsible for the alterations in representational awareness, sleep disturbance, perceptual distortions and affective bias in information processing seen in depressed patients, symptoms indicative of alterations in consciousness. Changes in cortisol (and/or DHEA) levels may underlie impairments in neuropsychological function, especially working memory, that may reflect the content of consciousness, and executive function, which some equate directly with consciousness itself. Increasing understanding of the neurochemical underpinnings of affective disorders may also provide information on the systems involved in the more enigmatic subject at the heart of human existence — consciousness.

References

Abbott, F.V. et al. (1992). *Psychopharmacology* 108, 60–66.

Aronsson, M. et al. (1988). *Proceedings of the National Academy of Sciences of the United States of America* 85, 9331–9335.

Atkinson, R.C. & R.M. Shiffrin (1971). *Scientific American* 225, 82–90.

Austin, M.-P. & P. Mitchell (1995). *Psychological Medicine* 25, 665–672.

Austin, M.-P. et al. (1992). *Journal of Affective Disorders* 25, 21–30.

Bahrainian, S.A. et al. (1995). *Journal of Psychopharmacology* 9(Suppl.), A4.

Banki, C.M. et al. (1992). *European Neuropsychopharmacology* 2, 107–113.

Barden, N. et al. (1995). *Trends in Neurosciences* 18, 6–11.

Benkelfat, C. et al. (1994). *Archives of General Psychiatry* 51, 687–697.

Blaney, P.H. (1986). *Psychological Bulletin* 99, 229–246.

Brody, J.F. (1978). *Psychopharmacology* 17, 14–33.

Brown, W.A. & C.B. Qualls (1981). *Psychiatry Research* 4, 115–128.

Budziszewska, B. et al. (1995). *Polish Journal of Pharmacology* 47, 299–304.

Caine, E.D. et al. (1984). *American Journal of Psychiatry* 141, 116–118.

Calogero, A.E. et al. (1990). *Endocrinology* 126, 1888–1894.

Calogero, A.E. et al. (1989). *Peptides* 10, 189–200.

Carli, M. et al. (1995). *Behavioural Brain Research* 67, 67–74.

Carroll, B.J. et al. (1981). *Archives of General Psychiatry* 38, 15–22.

Chalmers, D.T. et al. (1994). *Neuropsychopharmacology* 10, 215–222.

Christensen, H. et al. (1997). *Journal of the International Neuropsychological Society* 3, 631–651.

Cohen, R.M. et al. (1982). *Archives of General Psychiatry* 39, 593–597.

Cowen, P.J. et al. (1990). *Psychiatry Research* 31, 201–208.

de Quervain, D.J.F. et al. (2000). *Nature Neuroscience* 3, 313–314.

Deakin, J.F.W. & F.G. Graeff (1991). *Journal of Psychopharmacology* 5, 305–315.

Delacour, J. (1995). *Neuropsychologia* 33, 1061–1074.

Delgado, P.L. et al. (1990). *Archives of General Psychiatry* 47, 411–418.

Donald, M. (1995). *Neuropsychologia* 33, 1087–1102.

Drevets, W.C. et al. (2000). *Nuclear Medicine and Biology* 27, 499–507.

Elliott, R. (1998). *Trends in Cognitive Sciences* 2, 447–454.

Elliott, R. et al. (1996). *Psychological Medicine* 26, 975–989.

Ferrier, I.N. et al. (1991). *International Journal of Geriatric Psychiatry* 6, 279–286.

Ferrier, I.N. et al. (1999). *British Journal of Psychiatry* 175, 246–251.

Goodwin, G.M. et al. (1985). *Nature* 317, 531–533.

Goodwin, G.M. et al. (1992). *Journal of Affective Disorders* 26, 73–84.

Gray, J.A. (1995). *Neuropsychologia* 33, 1143–1153.

Harder, J.A. et al. (1996). *Psychopharmacology* (Berlin) 127, 245–254.

Heinrichs, S.C. et al. (1995). *Annals of the New York Academy of Sciences* 771, 92–104.

Ilsley, J.E. et al. (1995). *Journal of Affective Disorders* 35, 1–9.

Joels, M. & E.R. de Kloet (1992). *Neuroendocrinology* 55, 344–350.

Joels, M. et al. (1991). *Journal of Neuroscience* 11, 2288–2294.

Kaminska, M. et al. (2000). *Brain Research Bulletin* 52, 229–234.

Kelly, W.F. et al. (1983). *British Journal of Psychiatry* 142, 16–19.

Laaris, N. et al. (1995). *Neuropharmacology* 34, 1201–1210.

Le Corre, S. et al. (1997). *Psychopharmacology* 130, 368–374.

Linkowski, P. et al. (1985). *Journal of Clinical Endocrinology & Metabolism* 61, 429–438.

Markowitsch, H.J. (1995). *Neuropsychologia* 33, 1181–1192.

McAllister-Williams, R.H., et al. (2001). *International Journal of Neuropsychopharmacology.*

McAllister-Williams, R.H. et al. (1998). *Psychological Medicine* 28, 573–584.

McAllister-Williams, R.H. & A.H. Young (1998). In D. Ebert & K. Ebmeier (Eds.), *New models for depression* (170–198). Basel: Karger.

McEntee, W.J. & T.H. Crook (1991). *Psychopharmacology* 103, 143–149.

Nemeroff, C.B. (1996). *Molecular Psychiatry* 1, 336–342.

Nemeroff, C.B. et al. (1992). *Archives of General Psychiatry* 49, 384–387.

Nishi, M. & E.C. Azmitia (1996). *Brain Research* 722, 190–194.

Pare, D. & R. Llinas (1995). *Neuropsychologia* 33, 1155–1168.

Park, S.B. et al. (1994). *Neuropharmacology* 33, 575–588.

Perlis, M.L. et al. (1997). *Biological Psychiatry* 42, 904–913.

Porter, R.J. et al. (1998). *Psychopharmacology* 139, 243–250.

Power, A.C. & P.J. Cowen (1992). *Molecular Aspects of Medicine* 13, 205–220.

Price, L.H. et al. (1989). *Archives of General Psychiatry* 46, 625–631.

Price, L.H. et al. (1985). *Life Sciences* 37, 809–818.

Riedel, W.J. et al. (1999). *Psychopharmacology* 141, 362–369.

Rubin, R.T. et al. (1996). *Biological Psychiatry* 40, 89–97.

Rubinow, D.R. et al. (1984). *Archives of General Psychiatry* 41, 279–283.

Sachar, E.J. et al. (1973). *Archives of General Psychiatry* 28, 19–24.

Salomon, R.M. et al. (1993). *International Clinical Psychopharmacology* 8(Suppl 2), 41–46.

Sargent, P.A. et al. (2000). *Archives of General Psychiatry* 57, 174–180.

Schmitt, J.A. et al. (2000). *Journal of Psychopharmacology* 14, 21–29.

Seckl, J.R. & G. Fink (1991). *Journal of Steroid Biochemistry & Molecular Biology* 40, 685–688.

Shah, P. & A. Miyake (1999). In A. Miyake & P. Shah (Eds.), *Models of working memory: Mechanisms of active maintenance and executive control* (1–27). Cambridge: Cambridge University Press.

Shallice, T. (1988). *From neuropsychology to mental structure.* Cambridge: Cambridge University Press.

Smith, C.E. et al. (1991). *Psychopharmacology* 103, 140–142.

Smith, K.A. et al. (1997). *Lancet* 349, 915–919.

Starkman, M.N. et al. (1986). *Psychiatry Research* 19, 177–188.

Thase, M.E. (1998). *Journal of Clinical Psychiatry* 59(Suppl 4), 55–65.

Thase, M.E. et al. (1998). *Archives of General Psychiatry*, 55, 138–144.

Valzelli, L. & L. Pawlowski (1979). *Neuropsychobiology* 5, 121–128.

Veiel, H.O. (1997). *Journal of Clinical & Experimental Neuropsychology* 19, 587–603.

Watanabe, Y. et al. (1993). *Brain Research* 615, 87–94.

Wauthy, J. et al. (1991). *Biological Psychiatry* 30, 736–738.

Williams, J.M.G. & J. Scott (1988). *Psychological Medicine* 18, 689–695.

Winokur, G. et al. (1987). *Biological Psychiatry* 22, 360–368.

Wolkowitz, O.M. et al. (1990). *American Journal of Psychiatry* 147, 1297–1303.

Young, A.H. et al. (2000). *Biological Psychiatry* 47, S74.

Young, A.H. et al. (1999). *Psychopharmacology* 145, 260–266.

Young, A.H. et al. (1994). *Journal of Affective Disorders* 32, 139–146.

Young, S.N. et al. (1985). *Psychopharmacology* 87, 173–177.

Mental retardation and autism

Gregory O'Brien and Louise Barnard

1. Introduction

This chapter is concerned with the neurochemical basis of developmental disability which is considered here in two forms: the globally delayed or halted development seen in mental retardation, and the more circumscribed pattern of disordered development of autism. A range of deficits of important key aspects of consciousness are apparent in both conditions. Of particular relevance to consciousness are the cognitive and behavioural impairments in attention, concentration, memory, information processing and social behaviour which are commonly present. Consideration of aberrant neurotransmitter activities in these developmental deficits may provide insights into the role of neurotransmitters in consciousness.

2. Mental retardation

2.1 Definition and relevance to neurochemistry of consciousness

Mental retardation is the generic term for the condition of global developmental delay, characterised by significant impairment of intelligence (defined in IQ terms as under 70), social function and the capacity for self-care, where these have been present from birth or early in life (World Health Organisation, 1992, O'Brien, 2000a). Mental retardation is not a unitary condition, but includes developmentally-determined deficiencies in functioning, due to a wide variety of pre-, peri- and post-natal pathologies, which are shaped by a host of developmental and social influences (reviewed, O'Brien, 2000a). Common aetiologies include: genetic and chromosomal anomalies such as Down's syndrome, intrauterine infections and other toxic events, various types of cerebral

palsy, brain trauma, and meningitis in early childhood. The clinical manifestations of these conditions display wide variation, both between and within conditions, according to cause, nature, timing and site of developmental insult. This clinical heterogeneity is seen not only in the variety of physical, medical and overall intellectual disabilities which comprise the phenotypes of the causal syndromes of mental retardation, but also in the different patterns of cognition and behaviour (O'Brien & Yule, 1995; O'Brien, 2000b).

This diversity of mental retardation, in both cause and phenotype, carries important implications for consideration of the biochemistry of consciousness. On the one hand, because this is an investigation of multiple causalities—including, for example, inborn errors of metabolism, each of which has its own unique biochemical profile (Cook & Leventhal, 1996), it may not prove possible to identify specific neurotransmitter abnormalities which are common to mental retardation as such. On the other hand common themes concerning key neurotransmitters may be identified from studies of mental retardation. Altered neurotransmitter functioning associated with the severity of mental retardation is open to different interpretations, either reflecting fundamentally impaired development of cerebral structure or a more general impairment of central transmitter activity and functioning.

2.2 Neurotransmitter functioning

Two transmitters have been the subject of most studies in mental retardation: serotonin and dopamine and this section focuses on abnormalities in the function of these transmitters, and effects of serotonin- and dopamine-altering drugs.

2.3 Serotonergic abnormalities

Serotonin is the neurotransmitter most widely studied in mental retardation, with findings extending over the past 40 years. Schain and Freedman (1961) included mentally retarded children in their pivotal study, in which whole blood hyperserotonaemia (elevated levels of endogenous serotonin) was reported in a severely retarded, but not a mildly retarded group. Partington (1973) also found significantly elevated (above the 90th percentile) whole blood serotonergic levels (Partington et al., 1973); with females having even higher levels than males (Tu & Partington, 1972). However, hyposerotonaemia is associated with some specific syndromes, such as Cornelia de Lange syndrome, Down's

syndrome and phenylketonuria (Greenberg & Coleman, 1973; Pare, 1968; Tu & Partington, 1972).

Initially, it was thought that excess serotonin might be toxic to the brain and result in mental retardation. This explanation, which placed high neurotransmitter levels of serotonin as the key determinant, was favoured over other explanations, such as the high neurotransmitter levels being secondary to mental retardation. An analogy was drawn with phenylketonuria: without proper management, high levels of a central biochemical (phenylalanine) are toxic to people with this condition and result in mental retardation (Cook & Leventhal, 1996). Another key line of early evidence supporting putative serotonergic toxicity lay in the observation of an association between the extent of hyperserotonaemia and the severity of mental retardation. Hyperserotonaemia in mental retardation is more marked among more severely mentally retarded subjects (Hanley et al., 1977; Oikawa et al., 1978; Schain & Freedman, 1961). These early exploratory studies did not however take account of other factors associated with mental retardation, notably medication status and behaviour of subjects. As severe degrees of mental retardation correlate with more severely maladaptive behaviours and a greater prevalence of psychiatric disorders, one cannot distinguish whether the aetiology of the hyperserotonaemia relates to the mental retardation per se, or to the high rates of disturbed behaviour and psychiatric disorder (Takahashi et al., 1976; Hoshino et al., 1984; Gillberg & O'Brien, 2000). Although not conclusive, the association between degree of mental retardation and degree of hyperserotonaemia is nevertheless sufficiently corroborative of the hypothesis to warrant further exploration.

2.4 Effects of serotonin-altering drugs

The 5-HT$_{1a}$ agonist, buspirone, was administered to 8 mentally retarded patients with severe, long-lasting challenging behaviours (aggression, self-injury, impulsivity) (Verhoeven & Tuinier, 1996). Buspirone was effective in reducing behavioural disturbance and was associated with improvements in sociability. The tricyclic antidepressant clomipramine is effective at treating some associated behaviours of mental retardation, namely, stereotypies, hyperactivity, and irritability (Lewis et al., 1995). In this double-blind, placebo-controlled crossover trial, patients had severe or profound mental retardation. Stereotypic behaviours improved on two grounds: frequency and intensity. Clomipramine was also found to be effective in less severely retarded patients (mean IQ of 65), with particular target behaviours of obsessionality, compulsivity and ritualistic behaviours (Barak et al., 1995).

2.5 Dopaminergic abnormalities

Dopamine plays a key role in the regulation of cognition (Chapters 10 and 17) and control of movement. Given the abnormalities in these domains in mental retardation, any association between dopamine and mental retardation may be relevant to the neurochemistry of consciousness, especially relating to cognition.

Gillberg and Svennerholm (1987) assessed central dopaminergic functioning in mentally retarded children. They found that CSF (cerebrospinal fluid) levels of homovanillic acid (HVA: the primary metabolite of dopamine) were equivalent in mentally retarded and normal control groups. Garreau et al. (1988) measured urinary HVA (total, free and conjugated) and found higher urinary conjugated HVA concentrations in the mentally retarded group, as compared to a normal control group. These findings derived from studies that were primarily concerned with autism and other developmental disorders, using mentally retarded groups as controls. As with serotonin, there are issues of cause and effect in any identified association although further study of dopamine function in mental retardation appears to be warranted.

2.6 Effects of dopamine-altering drugs in mental retardation

Although controversial, the use of antipsychotics in mental retardation is extensive (Green, 1991). In general, these drugs do not treat the mental retardation, but rather the associated behavioural disturbances, particularly with respect to sleep, aggression and agitation. Haloperidol, a dopamine D_2 receptor antagonist, and pimozide, also a dopamine receptor antagonist, were given to a sub-group of mentally retarded patients in a cross-over study (Naruse et al., 1982). Although not significant, both tended to be superior to placebo.

3.   Autism

3.1 Definition and nature of autism

Autism is a major disorder of social and linguistic development which occurs in approximately 1 in 500 people in the general population (Gillberg, 1992). The condition is common among the mentally retarded, in whom at least 10% are affected (Gillberg et al., 1986; O'Brien, 2000a). Autism is defined by the pres-

ence of three features before the age of three years (World Health Organisation, 1992):

i)   Impaired social reciprocity: this refers to a lack of appreciation of the needs of others and results in autistic people appearing to be vague, detached, and not in empathic communion with others. Social developmental impairments are independent of intelligence, in that they are present in all autistic people.

ii) Delayed development of language: this must be pronounced to qualify as a diagnostic feature, but it can be varied in type. In some cases, there is no useful or functional language. In other cases, there is language, but it has a different quality consisting largely of repetition of phrases or words heard by the autistic individual. This echolalia is characteristically irrespective of context, and does not constitute meaningful verbal communication. Such marked disorder of language effectively results in the autistic individual being detached or socially aloof.

iii) Restricted, repetitive behaviour: often taking the form of apparent obsessional behaviour. In many individuals, this may be reflected in a preoccupation with sameness, and resultant extreme emotional upset if any routines or features in their surroundings are changed. In others, behaviour such as staring at spinning objects, or idiosyncratic focusing in on some part of an object, dominates.

3.2 Implications for the neurochemistry of consciousness

Autism is an interesting model for the study of consciousness. The combination of social isolation, language impairment and restricted, repetitive interests and behaviours together with idiosyncratic patterns in attention, concentration and interpersonal behaviour offer opportunities for the exploration of certain aspects of consciousness:

i)   Impaired social reciprocity: clearly, consciousness is a prerequisite for normal reciprocity to occur in any social functioning. Moreover, autistic individuals characteristically isolate themselves from others, such that their consciousness may be called into question by observers who are not familiar with the condition: for example, failing to respond to their name or appearing to be unaware of new people in their environment.

ii) Delayed development of language: normal language development requires conscious awareness, but lack of verbal language development may arise

from other major causes, such as deafness. In autism, verbal impairments are associated with impaired social reciprocity.

iii) Restricted, repetitive behaviour: occurring in the context of social aloofness and non-communication, repetitive behaviours may at first sight suggest that the individual is captivated in deep thought. However, from studies of higher functioning autistic people, there is some knowledge of the content and nature of thinking in this syndrome. Instead of a 'rich inner life' or a 'higher' consciousness, these behaviours represent a non-reflective, repetitive asocial style of thinking and doing.

3.3 Brain abnormalities

A coherent and comprehensive neuroanatomical basis for autism has as yet not been established, although inconsistent and diverse neurological abnormalities have been identified. The disparate findings may be due to the fact that autism is not one disease entity, but rather a behaviourally defined syndrome (Rapin, 1999). For example, at a gross anatomical level macrocrania and megalencephaly are apparent in a sub-set of people with this syndrome, but microcrania and microencephaly have also been reported (reviewed in Gillberg & Coleman, 2000). The only consistent gross structural abnormality to be reported is enlargement of the lateral ventricles in a sub-set of patients, notably those selected according to strict inclusion criteria (Minshew & Dombrowski, 1994). In the limbic system, cerebellum and inferior olive, abnormalities have been reported and subsequently replicated although on small samples, some of whom suffered from seizures and/or received anticonvulsant medication (Minshew et al., 1997; Bauman & Kemper, 1994). These findings are common in less mature normal brains, and may indicate an early curtailment of development.

3.4 Neurotransmitter functioning

If there is an association between the extent or severity of abnormal neurotransmitter functioning and the global measure of severity of autism, the direction and mechanism of causality may still be unclear (as has been discussed in mental retardation). However, neurotransmitter correlates of specific aspects of autism, such as social isolation or obsessional behaviour, are likely to be more revealing and of greater relevance to the study of consciousness.

3.5   Serotonergic abnormalities

The observation that serotonergic hallucinogens (e.g. LSD) could induce some autistic symptoms precipitated early work in this field. Schain and Freedman (1961) screened 23 autistic patients and discovered that 26% had whole blood hyperserotonaemia. Later results confirmed this observation; hyperserotonaemia has consistently been found in a quarter to a third of the autistic population (Cook & Leventhal, 1996; Herault et al., 1996; Anderson et al., 1987). The median reported increased group value is approximately 50% above the normal value (Anderson et al., 1990). Mean levels of CSF 5-hydroxyindoleacetic acid (5-HIAA, the primary serotonergic metabolite) have consistently been found to be equivalent in autistic individuals and healthy controls (Anderson, 1994). Gillberg and colleagues (Gillberg et al., 1983) performed lumbar punctures on 13 autistic children with varying degrees of mental retardation (12 of who were unmedicated) and age and sex matched healthy controls. Autistic children had slightly higher values of 5-HIAA, but the difference was not significant.

More than 99% of whole blood serotonin is contained in the platelets, and as such, hyperserotonaemia is thought to be attributable to platelet abnormalities (Cook & Leventhal, 1996). Several studies have sought to clarify the mechanism of this hyperserotonaemia. One possible explanation is an alteration in serotonin metabolism—either increased serotonin synthesis or decreased serotonin catabolism. The role of the serotonin precursor, tryptophan has been investigated in studies of the association of plasma tryptophan levels and central serotonergic functioning (Anderson & Hoshino, 1997). The focus was on levels of plasma free tryptophan, since this form influences tryptophan metabolism in the brain. Hoshino et al. (1984) compared plasma free tryptophan, total tryptophan and serotonin levels in the blood of 37 autistic and 67 normal controls. They found that plasma free tryptophan and whole blood serotonin concentrations were significantly higher in the autistic group, although there was no correlation between these two substances. Blood serotonin did not correlate with clinical rating scales or developmental quotient. Plasma free tryptophan elevations were positively correlated with the severity of maladaptive behaviour (as measured by the Children's Psychiatric Rating Scale) and tended to be positively correlated with hyperactivity. Croonenberghs et al., (2000) measured plasma concentrations of tryptophan, serum concentrations of serotonin and 24-hour urinary excretion of 5-HIAA in 13 autistic, post-pubertal males and 13 matched healthy controls. They found plasma tryptophan concentrations were significantly lower in the autistic sam-

ple than the healthy sample, but failed to find significant differences between serum serotonin and urinary 5-HIAA; they did not measure plasma free tryptophan. D'Eufemia et al. (1995) also found significantly lower tryptophan activity (assessed by comparing tryptophan to large neutral amino acid ratios) in a sample of 40 autistic children, as compared to 46 controls. The apparent disparity between the early reports of high levels of tryptophan and the more recent reports of low levels in autistic people can be largely explained by inadequately controlled studies and the use of heterogeneous samples. Abnormal levels of plasma tryptophan may be a feature of autism, but these may be as a consequence of hyperserotonaemia rather than cause.

Another mechanism of hyperserotonaemia may be increased serotonergic catabolism. Measurement of MAO (monoamine oxidase) the primary catabolic enzyme for serotonin, in urine or plasma provides an indication of serotonin catabolism. No differences have been found between autistic and control patients in platelet MAO activity (Anderson et al., 1990), although this area of research is somewhat compromised as MAO-A is the variant that primarily metabolises serotonin, whereas MAO-B is the form found in platelets (Anderson et al., 1990; Anderson & Hoshino, 1997). However, further evidence for normal catabolism comes from investigations concerning 5-HIAA. A medication controlled study found urinary 5-HIAA levels to be equivalent in non-medicated autistic individuals and age-matched controls (Minderaa et al., 1987) which confirmed findings of earlier work (Schain & Freedman, 1961), but was discordant with other findings (Hanley et al., 1977). Hanley et al. (1977) reported urinary 5-HIAA levels in hyperserotonaemic autistic people to be double that of mentally retarded controls. Further, when a tryptophan load was administered, 5-HIAA showed a greater increase in those with autism than in the controls. Caution is needed when interpreting these results: they might reflect peripheral levels of serotonin rather than CNS levels as most urinary and plasma 5-HIAA is derived from the gastrointestinal tract. Increased synthesis of serotonin may lead to hyperserotonaemia, but the observation of normal MOA and 5-HIAA levels, indicate that serotonin catabolism is normal in autism (Anderson et al., 1990).

Since no consistent differences in serotonergic catabolism or metabolism have been identified in autism, yet a substantial proportion of autistic people have increased concentrations of platelet serotonin, attention has turned to the platelets themselves. Platelet irregularities may include increased platelet exposure, increased platelet volume or enhanced platelet uptake and storage, of serotonin. By measuring the concentration of plasma free levels of serotonin, it is possible to assess whether the platelet is exposed to elevated lev-

els of serotonin. Exposure has been found to be equivalent in autistic patients and controls (Anderson, 1994). Decreased rates of platelet serotonin up-take in 'schizophrenic- autistic' children as compared to 'schizophrenic- non-autistic' children were reported in earlier studies (Sankar, 1970 and Sankar, 1977). Others have found uptake to be normal (Lucas et al., 1971; Yuwiler et al., 1975) or increased (Rotman et al., 1980; Katsui et al., 1986). An early report suggested that autistic people had a greater efflux rate of pre-loaded [^{3}H]-5-HT during in vitro incubation (Boullin et al., 1971). This observation fuelled a multi-centred research initiative, which failed to find any differences between an autistic and normal group (Boullin et al., 1982). Some of these studies are methodologically flawed as incubation periods were too extensive (Yuwiler et al., 1985) and distinctions between different types of efflux, such as active transport and passive diffusion, were not made (Anderson et al., 1990).

Consensus about the nature of serotonergic abnormalities is thus rare. Some researchers have analysed relationships between levels of hyperserotonaemia and the extent of disturbed behaviours. Overall severity of autism can be measured in a number of ways (reviewed O'Brien & Yule, 1995; O'Brien et al., 2001). One of the most widely employed is a simple checklist, which scores the occurrence of some of the most common and important features of the condition, the Autism Behaviour Checklist (ABC). In one study of 25 autistic boys (Kuperman et al., 1987) no correlation between concentration of serotonin and ABC scores was found. Other studies of the association between severity of autism and hyperserotonaemia have been more positive. Most of these investigations have been carried out in parallel with the effects of serotonin-altering drugs in autism. There is some evidence of an association, most notably in respect of certain behavioural domains. For example, there have been reports that there is a correlation between serotonergic status and levels of motor activity. Takahasti et al. (1976) reported that a high-motor activity autistic group had higher serotonin levels than a low-motor activity autistic group.

3.6 Effects of serotonin-altering drugs

There is compelling evidence that pharmacological agents which affect serotonin concentrations are effective in the autistic population. Fenfluramine was one of the first pharmacological treatments to be applied to autism. Fenfluramine is an indirect non-selective serotonin receptor agonist, which in the long-term causes a reduction in serotonin release. Fenfluramine efficacy was evaluated in a large multi-centre, single-blind study. In a report from nine of these centres involving 81 patients (Ritvo et al., 1986), significant improve-

ments in overall-autistic, motor, social and sensory measures of the Ritvo-Freeman Real-Life Rating Scale for Autism were reported, but there were no changes in mood, language or IQ (McDougle, 1997). These initial studies were highly encouraging, particularly in view of the apparent specificity of the effect and evidence that fenfluramine improves overall autistic symptoms, and also enhances motor activity, social behaviour and sensory functioning. However, in a double-blind study of fenfluramine (Campbell et al., 1988), there were significant decreases in stereotypies and fidgeting, but no effect on the core symptoms of autism. Moreover, this study found that fenfluramine also lowered performance on a discriminant learning task. The more powerfully designed studies (double-blind, placebo-controlled, balanced) thus failed to yield evidence of fenfluramine affecting core features of autism. Perry and Kuperman (1996) concluded that although fenfluramine reduces CNS serotonin, only a small minority of patients benefit from the drug.

The action of serotonin re-uptake inhibitors (including fluoxetine, fluvoxamine and sertraline), tricyclic antidepressant (including clomipramine and imipramine), receptor agonists (such as buspirone), and antagonists (e.g. methysergide) on overall autistic features and problem behaviours such as stereotypies, obsessions and concurrent mood and affective disorders have been widely investigated (McDougle, 1997). Some improvements are apparent which are secondary to effects on mood, or to related clinical features such as aggression, self-injury and obsessional behaviour. These findings support the proposition that the reported abnormalities of serotonin activity in autism are not reflections of core autism, but of certain behavioural manifestations of autism, such as generally disturbed, aggressive or over-active behaviour, and of concurrent psychiatric disorder.

There is as yet little evidence of specific association between abnormal serotonin activity and any of the key cognitive features of autism. More circumscribed study of particular cognitive functions of autism may yet yield new insights. Perhaps most promisingly, the findings of associations between serotonin functioning and obsessional behaviour indicate the need for further investigation.

3.7 Dopaminergic abnormalities

Dysfunction of the dopamine system has been implicated in autism. Abnormalities have been observed in levels of whole blood, urinary and CSF dopamine and HVA. Also dopamine antagonists alleviate some autistic symptoms. It is thought that the levels of the HVA in the CSF reflect central

dopamine turnover in the brain. As with serotonin, there are a limited number of studies measuring CSF dopamine and HVA in autism, because of the invasive nature of collecting these samples. The research that does exist is often contradictory. Gillberg and Svennerholm (1987) reported on 25 cases of infantile autism that had significantly higher concentrations of CSF HVA than did controls, and significantly elevated levels of HVA as compared to their 5-HIAA levels. However, Narayan et al. (1993) compared CSF concentrations of HVA and failed to find a significant difference between 17 autistic and 15 non-neurologically impaired controls.

Given the difficulties inherent in carrying out investigations of CSF dopamine, urinary HVA in autism has been investigated. In a study of 50 autistic children, Martineau et al. (1994) found that urinary dopamine was slightly lower and urinary HVA was slightly higher in the autistic group, than for age and sex matched normal control data. Whole blood assays revealed raised levels of dopamine in the autistic group, compared to control groups. However, Croonenberghs et al. (2000) found no significant differences between the 24-hour urinary dopamine concentrations of 13 post-pubertal, Caucasian autistic males and 13 matched controls. Garreau et al. (1988) found high levels of total urinary HVA in their autistic subjects. When the results for the autistic cases were sub-divided into those who were also mentally retarded and those who were not, the mentally retarded autistic group had elevated HVA levels relative to both normal and mentally retarded control groups, but this difference did not exist in the high-functioning (not mentally retarded) autistic people.

3.8 Effects of dopamine-altering drugs

Amphetamine, an indirect dopamine receptor agonist, exacerbates hyperactivity and stereotyped motor behaviours in autism (McDougle, 1997) implicating dopaminergic hyperactivity. Haloperidol is one of the most extensively studied drugs in the treatment of autism. It was initially found to be useful in this population by Campbell and colleagues (1978) in a double-blind placebo-controlled study, where reductions in stereotypic behaviour and in social withdrawal were found. These positive effects were subsequently replicated (Cohen et al., 1980; Anderson et al., 1984), and corroborated by improvements in hyperactivity, temper tantrums and social relatedness (Anderson et al., 1989). However, severe side effects, especially dyskinesias, have led most authorities to advise against its use in autism (McDougle, 1997). The efficacy of dopamine receptor antagonism corroborates the findings of high dopamine activity in autism.

Abnormalities in dopamine function in autism may provide new insights into the neurochemistry of consciousness. Assays of dopamine and HVA indicated, though not consistently, that dopamine activity is increased. The effects of the dopamine agonists are more convincing, in that motor problems are exacerbated, and concentration diminished by their administration. Also, dopamine receptor antagonists display a selective beneficial effect on behaviours in autism, notably on problem behaviours related to motor activity and on the cognitive domain—social cognition. These findings suggest that dopamine activity plays a key role in the expression of some of the major motor and cognitive features of autism.

3.9   Other transmitters

Other neurotransmitters have also been investigated in autism. Assessments of noradrenaline have so far failed to yield any convincing evidence that this transmitter is abnormal. CSF levels of noradrenaline have consistently been found to be normal in autistic groups (reviewed Anderson & Hoshino, 1997). Plasma levels of noradrenaline have been found to be elevated in autism (Lake et al., 1977; Launay et al., 1987), although paradoxically levels of the enzyme, dopamine-B-hydroxylase are low (Lake et al., 1977). Levels of plasma noradrenaline and its primary metabolite, MHPG (3-methoxy-4-hydroxyphenylglycol) are normal (Young et al., 1981), even when patients are unmedicated (Minderaa et al., 1994). Platelet concentrations of noradrenaline and adrenaline have however been found to be significantly lower than in controls (Launay et al., 1987). Drugs that affect noradrenergic function, particularly desipramine, clonidine and beta-blockers, have had some success in treating autistic symptoms (McDougle, 1997).

The role of neuropeptides has also been evaluated and it has been suggested that there are elevated levels of endogenous opioids. Assays of CSF beta-endorphin have given conflicting results: levels have been found to be respectively elevated, normal and decreased (Ross et al., 1987; Nagamitsu et al., 1997; Gillberg et al., 1990). Endogenous opioids are implicated in self-injurious behaviours- dysregulation of these may explain the presence of this phenomena in the autistic population. Further evidence for the possible role of opioids in the pathophysiology of autism derives from effects of the opiate receptor antagonist naltrexone, which has been useful in this population (Tsai, 1999; Cazzullo et al., 1999). A possible explanation for opioid abnormalities is a failure of the natural transition from production of stronger-longer acting endogenous opiates (beta-endorphin) to weaker, shorter acting endogenous opiates,

which usually occurs with age, thus resulting in elevated endogenous opioids (Panksepp, 1979).

The peptide, melatonin, has been implicated in autism. Excess melatonin is thought to decrease learning, memory, attention, emotionality, motivation and pain responses (reviewed Chamberlain & Herman, 1990)—all behaviours that are abnormal in autism. Melatonin, released from the pineal gland, is implicated in controlling serotonin and POMC (proopiomelanocortin) peptides, such as beta-endorphin, and an elevation may contribute to, or cause, the serotonin and opioid abnormalities (Chamberlain & Herman, 1990).

Recent research has indicated select abnormalities in the cholinergic system (Perry et al., 2001). Although previously unexamined neurochemically, there was an indication that the cholinergic system may be involved in autism, with abnormalities reported in neurons in the basal forebrain (Bauman & Kemper, 1994). Perry et al. (2001) found extensive loss of high affinity nicotinic receptors from the neocortex (frontal and parietal), and from the cerebellum (Lee, et al., in preparation). Nicotinic receptors are implicated in attention, and also consciousness as many general anaesthetics block the receptor channel (Chapter 9).

4. Summary

The empirical observations that initiated this review are that certain deficits in cognition and behaviour, which occur in developmental disability, relate to abnormalities in consciousness. Two types of developmental disability have been considered: mental retardation and autism. In mental retardation, hyperserotonaemia has been reported, but this is also related to other factors, including behaviour disorder. Also, in mental retardation, raised levels of dopamine have been reported, but not consistently, and the significance here is less certain. Studies of serotonin and dopamine activity in autism have been more productive. Hyperserotonaemia is an established feature of a substantial minority of autistic people, where it is a marker of a clinical subtype, characterised by activated, disturbed behaviour. Studies of serotonin- altering drugs in autism corroborate this finding, but the mechanism involved is as yet unclear. Raised levels of dopamine have also been reported in autism, and may be implicated in the obsessional behaviour of autistic people, and in their social withdrawal. Although far from certain, the results of some studies of dopamine-altering drugs are consistent with such a role. It seems likely that one route towards an understanding of the neurochemical basis of consciousness will be through

further studies on the association between autism and serotonin, dopamine and potentially acetylcholine.

References

Anderson, G.H. (1994). In M.L. Bauman & T.L. Kemper (Eds.), *The Neurobiology of Autism* (227–242). Baltimore: John Hopkins University Press.

Anderson, G.M. et al. (1987). *Journal of Child Psychology & Psychiatry & Allied Disciplines* 28, 885–900.

Anderson, G.M. et al. (1990). *Annals of the New York Academy of Sciences* 600, 331–342.

Anderson, G.M. & Y. Hoshino (1997). In D.J. Cohen & F.R. Volkmar (Eds.), *Handbook of Autism and Pervasive Developmental Disorders* (325–343). USA: Wiley.

Anderson, L.T. et al. (1989). *Journal of Autism & Developmental Disorders* 19, 227–239.

Anderson, L.T. et al. (1984). *American Journal of Psychiatry* 141, 1195–1202.

Barak, Y. et al. (1995). *Journal of Clinical Psychiatry* 56, 459–461.

Bauman, M.L. & T.L. Kemper (1994). In M.L. Bauman & T.L. Kemper (Eds.), *The Neurobiology of Autism* (119–145). Baltimore: John Hopkins University Press.

Boullin, D. et al. (1982). *Journal of Autism & Developmental Disorders* 12, 97–98.

Boullin, D.J. et al. (1971). *Journal of Autism & Childhood Schizophrenia* 1, 63–71.

Campbell, M. et al. (1988). *Journal of the American Academy of Child & Adolescent Psychiatry* 27, 434–439.

Campbell, M. et al. (1978). *American Academy of Child Psychiatry* 17, 640–655.

Cazzullo, A.G. et al. (1999). *European Neuropsychopharmacology* 9, 361–366.

Chamberlain, R.S. & B.H. Herman (1990). *Biological Psychiatry* 28, 773–793.

Cohen, I.L. et al. (1980). *American Academy of Child Psychiatry* 19, 665–677.

Cook, E.H. & B.L. Leventhal (1996). *Current Opinion in Pediatrics* 8, 348–354.

Croonenberghs, J. et al. (2000). *Neuropsychopharmacology* 22, 275–283.

D'Eufemia, P. et al. (1995). *Biomedicine & Pharmacotherapy* 49, 288–292.

Garreau, B. et al. (1988). *Developmental Medicine & Child Neurology* 30, 93–98.

Gillberg, C. (1992). *Journal of Child Psychology & Psychiatry* 33, 813–842.

Gillberg, C. & M. Coleman (2000). *The Biology of the Autistic Syndromes*. Cambridge: Mac Keith Press.

Gillberg, C. & G. O'Brien (Eds.) (2000). *Developmental Disability & Behaviour*. Clinics in Developmental Medicine number 149, London: Mac Keith Press.

Gillberg, C. et al. (1986). *British Journal of Psychiatry* 149, 68–74.

Gillberg, C. & L. Svennerholm (1987). *British Journal of Psychiatry* 151, 89–94.

Gillberg, C. et al. (1983). *Journal of Autism & Developmental Disorders* 13, 383–396.

Gillberg, C. et al. (1990). *Brain Development* 12, 88–92.

Green, W.H. (1991). *Child & Adolescent Clinical Psychopharmacology*. USA: Williams & Wilkins.

Greenberg, A. & M. Coleman (1973). *Pediatrics* 52, 720–724.

Hanley, H.G. et al. (1977). *Archives of General Psychiatry* 34, 521–531.

Herault, J. et al. (1996). *Psychiatry Research* 65, 33–43.

Hoshino, Y. et al. (1984). *Neuropsychobiology* 11, 22–27.

Katsui, T. et al. (1986). *Journal of Autism & Developmental Disorders* 16, 69–76.

Kuperman, S. et al. (1987). *Journal of Autism & Developmental Disorders* 17, 133–140.

Lake, C.R. et al. (1977). *Archives of General Psychiatry* 34, 553–556.

Launay, J.M. et al. (1987). *Journal of Autism & Developmental Disorders* 17, 333–347.

Lewis, M.H. et al. (1995). *American Journal of Mental Retardation* 100, 299–312.

Lucas, A.R. et al. (1971). *Biological Psychiatry* 3, 123–128.

Martineau, J. et al. (1994). *Developmental Medicine & Child Neurology* 36, 688–697.

McDougle, C.J. (1997). In D.J. Cohen & F.R. Volkmar (Eds.), *Handbook of Autism and Pervasive Developmental Disorders* (707–729). USA: Wiley.

Minderaa, R.B. et al. (1994). *Biological Psychiatry* 36, 237–241.

Minderaa, R.B. et al. (1987). *Biological Psychiatry* 22, 933–940.

Minshew, N.J. & S.M. Dombrowski (1994). In M.L. Bauman & T.L. Kemper (Eds.), *The Neurobiology of Autism* (66–85). Baltimore: John Hopkins University Press.

Minshew, N.J. et al. (1997). In D.J. Cohen & F.R. Volkmar (Eds.), *Handbook of Autism and Pervasive Developmental Disorders* (344–369). USA: Wiley.

Nagamitsu, S. et al. (1997). *Journal of Autism & Developmental Disorders* 27, 155–163.

Narayan, M. et al. (1993). *Biological Psychiatry* 33, 630–635.

Naruse, H. et al. (1982). *Acta Paedopsychiatrica* 48, 173–184.

O'Brien, G. (2000a). In C. Gillberg & G. O'Brien (Eds.), *Developmental Disability and Behaviour* (12–26). London: Mac Keith Press.

O'Brien, G. (2000b). Behavioural phenotypes, *Journal of the Royal Society of Medicine* 93, 618–620.

O'Brien, G. et al. (2001). Supplement to *Developmental Medicine & Child Neurology*, in press.

O'Brien, G. & W. Yule (Eds.) (1995). *Behavioural Phenotypes.* Clinics in Developmental Medicine number 138, London: Mac Keith Press.

Oikawa, K. et al. (1978). *Life Sciences* 23, 45–47.

Panksepp, J. (1979). *Trends in Neuroscience* 2, 174–177.

Pare, C.M. (1968). *Advances in Pharmacology* 6, 159–165.

Partington, M.W. et al. (1973). *Developmental Medicine & Child Neurology* 15, 616–627.

Perry, E.K. et al. (2001). *American Journal of Psychiatry*, in press.

Perry, P. & S. Kuperman (1996). *Pediatric Psychopharmacology: Autism.* Virtual Hospital, Electronic source, Accessed February, 2001.

Rapin, I. (1999). *The American Academy of Neurology* 52, 902–904.

Ritvo, E.R. et al. (1986). *Psychopharmacology Bulletin* 22, 133–140.

Ross, D. et al. (1987). *Pediatric Neurology* 3, 83–86.

Rotman, A. et al. (1980). *Psychopharmacology* 67, 245–248.

Sankar, D.V. (1970). *Acta Paedopsychiatrica* 37, 174–182.

Sankar, D.V. (1977). *Neuropsychobiology* 3, 234–239.

Schain, R. J. & D.X. Freedman (1961). *The Journal of Pediatrics* 58, 315–320.

Takahashi, S. et al. (1976). *Journal of Autism & Childhood Schizophrenia* 6, 317–326.

Tsai, L.Y. (1999). *Psychosomatic Medicine* 61, 651–665.

Tu, J. & M.W. Partington (1972). *Developmental Medicine & Child Neurology* 14, 457–466.

Verhoeven, W.M. & S. Tuinier (1996). *Journal of Intellectual Disability Research* 40, 502–508.

World Health Organisation (1992). *The ICD–10 Classification of Mental and Behavioural Disorders*. Geneva, Switzerland: World Health Organisation.

Young, J.G. et al. (1981). *Life Sciences* 28, 2837–2845.

Yuwiler, A. et al. (1985). In E. Lajtha (Ed.), *Handbook of Neurochemistry*. New York: Plenum Press.

Yuwiler, A. et al. (1975). *Journal of Autism & Childhood Schizophrenia* 5, 83–98.

Envoi

This book has been for the Editors and many of the authors, something of an adventure or journey into the unknown. Contributors were invited to explore the subject of consciousness from their particular perspective of research or clinical practice relating to neurotransmitters. The outcome was by no means certain at the beginning, but in the end we have been rewarded with novel perspectives and an irresistible urge to venture further. A brief after-word or Envoi is warranted to consider how the various new ideas and information in the book could stimulate further exploration of transmitter-based neural correlates of consciousness (NCC). The Envoi is based on testable hypotheses that could in principle be investigated using currently available tools, and also highlights some important areas of omission in the present text.

One or more transmitter correlate?

It would be difficult to argue that no transmitter system is relevant; a key issue is whether just one, or a select few, are more central than the entire repertoire of transmitter systems. The case for acetylcholine as an essential NCC is most frequently made (Chapters 1, 2, 13, 14 and 16). The question of whether the basal forebrain or brainstem system is more important depends on whether it is accepted that consciousness during dreaming, however different, involves the same mechanism that underpins waking consciousness. If so, then because the brainstem system is inactive during non REM sleep when dreaming occurs, the forebrain system appears paramount. This system may sustain a background of relatively 'undifferentiated' consciousness, with the mode being influenced by the transition from tonic to phasic impulses and/or activity of additional transmitter systems.

The dopaminergic system is probably the next most popular contender on account of the continuous firing of mesolimbic neurons during the entire sleep/wake cycle (Chapter 7), and involvement of this system in schizophrenia, Parkinson's disease, and more controversially autism (Chapters 15, 17 and 19), together with the actions of neuroleptics (Chapter 11). While not per-

haps a core correlate, dopamine may set the 'pace' of conscious information processing. Other modulatory transmitters are arguably not so obviously essential for consciousness, since they are inactive during REM sleep, although such systems as 5-HT and noradrenaline clearly contribute to the more rational or logical nature of waking, as opposed to dream, mentation (Chapters 3 and 8). The importance of the 5-HT system is also highlighted in relation to mood and alterations in consciousness in autism (Chapters 18 and 19), and on the basis of drug effects that suggest this transmitter may be relevant in setting the boundaries between 'self' and 'non-self' awareness (Chapter 13). The noradrenergic system by comparison has been relatively neglected, despite its central role in arousal (Chapter 3). The Chapters on attention, memory and motivation (3–5) draw attention to the variety of transmitters which are implicated in these components of consciousness that may be necessary but not sufficient.

Variations in consciousness may be sub-served by different combinations of transmitter activities. For example, together with forebrain acetylcholine, noradrenaline is likely to control the level of attention, dopamine the degree of motivation, and glutamate the involvement of memory. The focus in most chapters has been modulatory transmitter systems which Edelman (2000) has referred to as 'value' systems. There has been less emphasis on glutamate and GABA. Yet GABA is clearly involved in modulating the level of consciousness as in sleep and the action of some general anaesthetics. Its synthetic enzyme, glutamate decarboxylase has long been known to be selectively affected in the human brain as a result of coma—frustrating attempts investigate the GABA system in disease using autopsy brain tissue. Coma is incidentally one of the obvious topic omissions in the book. With respect to glutamate, it has recently been suggested that coherence between incoming and re-entrant signalling, which is thought to be required for conscious perception, is supported by the NMDA receptor channel; the receptor functioning as a coincidence detector between incoming signals (which remove inhibitory effects of magnesium) and re-entrant information (which releases glutamate) (Freitas de Rocha et al., 2001).

An obvious means of establishing the validity of potential transmitter NCC is the application of in vivo neurochemical imaging (PET, SPECT or MR spectroscopy) using available functional markers for the transmitters, their transporters, enzymes or receptors. If for example the cholinergic hypothesis is valid, pre-synaptic cholinergic activities and muscarinic or nicotinic receptor occupancy should increase in key cortical and thalamic areas during conscious processing. Such imaging analyses would extend the many already published on regional cerebral blood flow or metabolism. These would however also have

to meet the challenge levelled at existing imaging studies that, since conscious awareness involves numerous supportive cerebral activities, imaging indices need to be specifically related to consciousness.

Necessary and sufficient?

"Ideally we need to test for whether the NCC in question is both necessary and sufficient for the existence of consciousness. To establish necessity, we find out whether a subject who has the putative NCC removed thereby loses consciousness; to establish sufficiency, we find out whether an otherwise unconscious subject can be brought to consciousness by inducing the NCC" (Searle, 2001).

Models of 'putative NCC removal' in the human brain explored in several chapters include diseases in which particular transmitter systems or their activities are lost, or consequences of specific antagonist drugs. Again the major challenge is distinguishing effects on conscious awareness from all the other effects of such disturbances. Most discussions of disease states (Chapters 14–19) are inferential partly because until now, with the exception of dementia with Lewy bodies, little attention has been paid to how these specifically affect consciousness. However, tools are available to examine effects of disease on conscious awareness; detailed assessments of explicit as opposed to implicit attention or perception, for example. Deficits of acetylcholine, 5-HT and noradrenaline in AD and DLB, or of dopamine in PD (Chapters 14–16), could be examined from this perspective, as could the effects of drug therapies aimed at rectifying such deficits. While some of the most common neuropsychiatric diseases have been included in this book, there is clearly scope for considering many other disorders, for example: epilepsy, narcolepsy, attention deficit disorder, frontotemporal dementia, progressive supranuclear palsy, Huntington's disease and even personality disorders.

Amongst the different drug effects discussed (Chapters 9–13), the most relevant to essential mechanisms of conscious awareness are likely to be those which abolish consciousness. No unitary mechanism of general anaesthesia is apparent amongst the range of anaesthetic drugs, although nicotinic channel modification is common to many (Chapter 9). While abolishing cholinergic neurotransmission results in a loss of consciousness which is reversed by cholinergic agonists, consciousness can also be abolished by interfering with glutamate or GABA transmission. In this more catholic view of transmitter correlates, it is interesting that one of the principal mechanisms implicated in

natural sleep—adenosinergic transmission (Chapter 6)—has apparently been neglected in research into potential mechanisms of anaesthesia.

Closely related to mechanisms of anaesthesia in providing insights into neurochemical NCC is the neuropharmacology of hypnotics (Chapter 10). Hypnotic agents are neurochemically diverse and while reducing the level of conscious awareness, there are still degrees of conscious awareness during both REM and non REM sleep, with the ability to respond to at least some forms of sensory stimuli. Drug induced hypnosis, hallucinations and delirium (Chapters 10 and 12) involve a broad spectrum of transmitter pharmacology, no doubt reflecting the fact that disturbances in any of the principle transmitter systems can give rise to distortions in consciousness.

Correlating NCC

If specific neurotransmitters are to be considered as potential NCC, there should be links with other NCC. Nancy Woolf (Chapter 2) proposes a link between cholinergic transmission and microtubule quantum events, considered by some to provide a 'binding' mechanism underlying consciousness. Amongst other NCC, high frequency oscillation coincidence and synchronicity is commonly considered to be a potential 'binding' mechanism. It has however been suggested that electrophysiological mechanisms of subconscious information processing may not differ substantially from conscious awareness (Bradzil et al., 2001). There is nevertheless scope for investigating how manipulation of neurotransmission influences such oscillations. Such experiments could involve recording electrodes in lesioned or pharmacologically manipulated animal models of temporal binding in sensory awareness. In man, electrocorticographic recordings indicate that perception (auditory) induces gamma activity not only at 40Hz but also in higher gamma frequencies that appear to be an index of cortical activation reflecting task specific processing (Crone et al., 2001). In vitro, it has already been demonstrated that 40 Hz synchronicity can be induced in hippocampal slices by acetylcholine and subsequently blocked by atropine (Fisahn et al., 1998), suggesting that the muscarinic is the more important cholinergic receptor type (Chapter 2). Since such synchronicity is also apparent in vivo between cortex and thalamus, transmitter activities in key thalamic nuclei such as the reticular and intralaminar need to be considered in more detail.

Another popular concept of consciousness that may relate to neurotransmission is the importance of recurrent, versus feed forward, processing. Ac-

cording to Lammet and Roerfsema (2000), feed forward relay relates to processes that are hard wired and incapable of generating conscious awareness, whereas recurrent circuitry, depending on horizontal connections providing feedback, is necessary for an object to enter consciousness. Grossberg (1999) has also suggested that 'binding' may be a resonance or matching between top-down and bottom-up information processing. Attractive ideas such as these, similar to that proposed in relation to glutamate function (above), could no doubt be integrated into some of the many frameworks of reciprocal connections, or 'loop' circuitry involving relays between transmitter-specific neuron types in different brain areas (e.g. limbic, thalamo-cortical, and striato-cortical).

Conscious modelling of brain circuitry?

One of the obvious omissions in the book is the absence of any reference to the normal developing brain. A great deal is known about the sequence of expression, over-expression and subsequent pruning of synaptic markers, including transmitter activities, that occurs pre- and post-natally, This could provide new insights into transmitter NCC of emerging consciousness in the developing brain. Conscious awareness, reflection or recollection is probably apparent relatively soon after birth in man. It would be interesting to identify alterations in transmitter system activities in the human brain coinciding with this period.

Since trophic actions of transmitters and stimulation by transmitters of neurotrophin synthesis, which govern synaptic and dendritic morphology, are important not only during development but also in the adult brain, another intriguing question is whether conscious mental activity is associated with a distinct type of synaptic modelling or plasticity. There is evidence from brain damaged patients that cross-modal activation of brain areas deprived of their normal input requires the attention of the subject. If conscious mental activity does have longer term functional and structural consequences, which differ from those associated with non conscious information processing, this would add a new dimension to the adage, 'I think therefore I am', and perhaps also new insights for cognitive therapies.

While the function of REM sleep is unknown, it has been speculated that since this is abundant perinatally and declines to a much lower level at maturity, such periodic brain activation during sleep is required to establish and maintain synaptic connectivity. As emphasised in Chapters 6–8, the principle distinction between non REM and REM sleep, in terms of transmitter activa-

tion, is increased firing of cholinergic projection pathways from the brain stem and basal forebrain. Neurotrophic functions of cholinergic transmission may be mandatory, and periodic activation during sleep essential to the structural integrity of neuronal connections. If so, REM abnormalities that occur in degenerative diseases such as AD, PD and DLB (Chapters 14–18) could contribute to the neurodegeneration, and pharmacotherapy aimed at restoring normal REM sleep could be regenerative.

Distinguishing conscious from subconscious

In searching for mechanisms of consciousness, contrasting NCC with correlates of non conscious activities is likely to provide important insights. Transmitter mechanisms of subconscious or implicit activities have not generally been discussed in the book, although clearly neurotransmission is equally central. Distinctions between information processing that is explicit or conscious, on the one hand, and implicit, subliminal or subconscious, on the other hand, can be generalised : implicit as vast, parallel, rapid and rapidly decaying, feed forward, analytical, non-flexible or 'hardwired'; and explicit as restricted. linear, slower but increasing with time, feedback or recurrent, inferential, flexible or programmable. Characteristics of neurotransmission that might match such distinctions have not been addressed. The discrete localisation of modulatory as opposed to ubiquity of executive transmitters is, as argued in Chapter 1, consistent with the restricted nature of the conscious 'stream'. The extreme rapidity of ligand-gated ion channel receptor opening and desensitisation, contrasting with the slower and longer lasting response of metabotropic receptors could implicate metabotropic transmission as the more relevant for conscious processing. In terms of flexibility and recurrent or feedback mechanisms which link neuronal firing to synaptic remodelling, these are, as postulated in learning and memory, likely to involve release of neurotrophins and other synaptic and dendritic modulators as a result of concomitant pre-synaptic and post-synaptic neuronal activity.

The distinction between conscious and subconscious mentation may however be more a matter of degree than absolute divide. This is most obvious in the transition from waking to normal sleep and dreaming. The neurochemistry of dreaming may ultimately provide one of the most important clues as to the chemistry of consciousness. In addition the basis of some mental disorders may be, as proposed for schizophrenia for example, the intrusion of dreaming mentation into the awake state. According to Allan Hobson's de-

scription of dreaming (Hobson, 1988): "We see things that aren't there (we hallucinate), believe things that could not possibly be true (we are deluded), become confused about time, place and person (we are disorientated), experience intense and wildly fluctuating emotion (we are affectively labile), and then conveniently forget the whole thing (we are amnesic)." Triggered by dramatic changes in chemical neurotransmission, this state of consciousness is a fairly accurate description of that in a variety of mental disorders.

In Summary

This book adds to numerous preceding texts on consciousness the relatively new concept that particular neurotransmitters may be central to the process. As outlined in the Preface, communication between neurons is essential for consciousness and such communication, on the timescale applicable to conscious perception, is principally mediated by chemical neurotransmission. As Susan Greenfield (2000) points out in 'The Private Life of the Brain', acetylcholine may enable "a whole population of cells to become more important than individual units, a kind of neuroscientific Marxism!" If the concept of transmitter NCC is incorporated into future discussions of the neurobiology of consciousness, or adds a further dimension to the neuropharmacology of disorders of the brain which affect conscious awareness, this book will have more than served its purpose.

Finally, although most of this book addresses the question of how neurotransmission might underpin consciousness, the relationship is no doubt reciprocal. Another perspective that might be explored in the future is how conscious awareness itself modulates neurotransmission. In James Austin's book 'Zen and the brain', he speculates as a neuroscientist and practitioner of Zen meditation, on whether cholinergic transmission is affected by meditative techniques such as kensho (an enlightened state reached after years of training): "Within the early seconds of a surge of acetylcholine, the slower muscarinic ACH receptor also starts to phase in. The effect continues for another 20 seconds or so. The inestimable time during which kensho evolved seemed to fall within this interval, as best one could guess." Future insights into how neurotransmitter NCC might contribute to understanding as yet unknown mechanisms of consciousness, will no doubt depend on similar moments of enlightenment.

Elaine Perry, Heather Ashton and Allan Young

References

Austin, J.H. (1998). *Zen and the brain.* Cambridge, Massechusetts: MIT Press.

Bradzil, M. et al. (2001). *Clinical Neurophysiology* 112, 650–661.

Crone, N.E. et al. (2001). *Clinical Neurophysiology* 112, 565–582.

Freitas de Rocha, F. et al. (2001). *Progress in Neurobiology* 64, 555–573.

Edelman, G.M. (2000). *Consciousness. How matter becomes mind.* London: Allen Lane.

Fisahn, A. et al. (1998). *Nature* 394, 186–194.

Greenfield, S. (2000). *The private life of the brain.* London: Penguin Books.

Grossberg, S. (1999). *Consciousness and Cognition* 8, 1–44.

Hobson, A. (1998). *The dreaming brain.* London: Penguin Books.

Lamme, V.A. & P.R. Roelfsema (2000). *Trends in Neurosciences* 23, 571–579.

Searle, J.R. (2000). *Annual Review of Neuroscience* 23, 557–578.

Index

In the series ADVANCES IN CONSCIOUSNESS RESEARCH (AiCR) the following titles have been published thus far or are scheduled for publication:

1. GLOBUS, Gordon G.: *The Postmodern Brain.* 1995.
2. ELLIS, Ralph D.: *Questioning Consciousness. The interplay of imagery, cognition, and emotion in the human brain.* 1995.
3. JIBU, Mari and Kunio YASUE: *Quantum Brain Dynamics and Consciousness. An introduction.* 1995.
4. HARDCASTLE, Valerie Gray: *Locating Consciousness.* 1995.
5. STUBENBERG, Leopold: *Consciousness and Qualia.* 1998.
6. GENNARO, Rocco J.: *Consciousness and Self-Consciousness. A defense of the higher-order thought theory of consciousness.* 1996.
7. MAC CORMAC, Earl and Maxim I. STAMENOV (eds): *Fractals of Brain, Fractals of Mind. In search of a symmetry bond.* 1996.
8. GROSSENBACHER, Peter G. (ed.): *Finding Consciousness in the Brain. A neurocognitive approach.* 2001.
9. Ó NUALLÁIN, Seán, Paul MC KEVITT and Eoghan MAC AOGÁIN (eds): *Two Sciences of Mind. Readings in cognitive science and consciousness.* 1997.
10. NEWTON, Natika: *Foundations of Understanding.* 1996.
11. PYLKKÖ, Pauli: *The Aconceptual Mind. Heideggerian themes in holistic naturalism.* 1998.
12. STAMENOV, Maxim I. (ed.): *Language Structure, Discourse and the Access to Consciousness.* 1997.
13. VELMANS, Max (ed.): *Investigating Phenomenal Consciousness. Methodologies and Maps.* 2000.
14. SHEETS-JOHNSTONE, Maxine: *The Primacy of Movement.* 1999.
15. CHALLIS, Bradford H. and Boris M. VELICHKOVSKY (eds.): *Stratification in Cognition and Consciousness.* 1999.
16. ELLIS, Ralph D. and Natika NEWTON (eds.): *The Caldron of Consciousness. Motivation, affect and self-organization – An anthology.* 2000.
17. HUTTO, Daniel D.: *The Presence of Mind.* 1999.
18. PALMER, Gary B. and Debra J. OCCHI (eds.): *Languages of Sentiment. Cultural constructions of emotional substrates.* 1999.
19. DAUTENHAHN, Kerstin (ed.): *Human Cognition and Social Agent Technology.* 2000.
20. KUNZENDORF, Robert G. and Benjamin WALLACE (eds.): *Individual Differences in Conscious Experience.* 2000.
21. HUTTO, Daniel D.: *Beyond Physicalism.* 2000.
22. ROSSETTI, Yves and Antti REVONSUO (eds.): *Beyond Dissociation. Interaction between dissociated implicit and explicit processing.* 2000.
23. ZAHAVI, Dan (ed.): *Exploring the Self. Philosophical and psychopathological perspectives on self-experience.* 2000.
24. ROVEE-COLLIER, Carolyn, Harlene HAYNE and Michael COLOMBO: *The Development of Implicit and Explicit Memory.* 2000.
25. BACHMANN, Talis: *Microgenetic Approach to the Conscious Mind.* 2000.
26. Ó NUALLÁIN, Seán (ed.): *Spatial Cognition. Selected papers from Mind III, Annual Conference of the Cognitive Science Society of Ireland, 1998.* 2000.
27. McMILLAN, John and Grant R. GILLETT: *Consciousness and Intentionality.* 2001.

28. ZACHAR, Peter: *Psychological Concepts and Biological Psychiatry. A philosophical analysis.* 2000.
29. VAN LOOCKE, Philip (ed.): *The Physical Nature of Consciousness.* 2001.
30. BROOK, Andrew and Richard C. DeVIDI (eds.): *Self-reference and Self-awareness.* 2001.
31. RAKOVER, Sam S. and Baruch CAHLON: *Face Recognition. Cognitive and computational processes.* 2001.
32. VITIELLO, Giuseppe: *My Double Unveiled. The dissipative quantum model of the brain.* 2001.
33. YASUE, Kunio, Mari JIBU and Tarcisio DELLA SENTA (eds.): *No Matter, Never Mind. Proceedings of Toward a Science of Consciousness: Fundamental Approaches, Tokyo, 1999.* 2001.
34. FETZER, James H.(ed.): *Consciousness Evolving.* n.y.p.
35. Mc KEVITT, Paul, Seán Ó NUALLÁIN and Conn Mulvihill (eds.): *Language, Vision, and Music. Selected papers from the 8th International Workshop on the Cognitive Science of Natural Language Processing, Galway, 1999.* n.y.p.
36. PERRY, Elaine, Heather ASHTON and Allan YOUNG (eds.): *Neurochemistry of Consciousness. Neurotransmitters in mind.* 2001.
37. PYLKKÄNEN, Paavo and Tere VADÉN (eds.): *Dimensions of Conscious Experience.* 2001.
38. SALZARULO, Piero and Gianluca FICCA (eds.): *Awakening and Sleep-Wake Cycle Across Development.* n.y.p.
39. BARTSCH, Renate: *Consciousness Emerging. The dynamics of perception, imagination, action, memory, thought, and language.* n.y.p.
40. MANDLER, George: *Consciousness Recovered. Psychological functions and origins of conscious thought.* n.y.p.
41. ALBERTAZZI, Liliana (ed.): *Unfolding Perceptual Continua.* n.y.p.